Maternal diabetes during pregnancy – obstetrical considerations and long term effects

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Maternal Diabetes during Pregnancy

Obstetrical considerations and long term effects

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Abstract

Maternal diabetes mellitus (DM) during pregnancy has detrimental health impacts on both the mother and fetus, and include increased risks of cardiac malformations, cesarean section (CS), and asphyxia. The aim of the thesis was to investigate short and long term cardiac effects after fetal exposure to DM, investigate the ability of a 5 minute Apgar score as a marker for obstetrical care, investigate the association between mode of delivery in diabetic pregnancies and a low 5 minute Apgar score, and to investigate the association between offspring birth weight and maternal risk of future DM.

Paper 1: Fetuses to mothers with either type 1 DM ($p = 0.0015$) and gestational diabetes mellitus (GDM) ($p = 0.006$) showed increased pulsatility index in the ductus venosus (PI-DV) in relation to gestational age. After the exclusion of SGA fetuses and those with blood flow changes, the PI-DV was still increased in type 1 DM ($p = 0.02$) and GDM pregnancies ($p = 0.035$), presumably reflecting short term cardiac impact.

Paper 2: Fetuses exposed to type 1 DM showed an increased risk of future cardiovascular disease, as measured by consumption of drugs for cardiovascular disease, OR 1.46 (95% CI 1.16-1.83), this increased risk was however no longer present when data was adjusted for offspring with insulin dependent DM, OR 1.22 (95% CI 0.97-1.54). As previous studies have showed, an increased risk of future cardiovascular disease was found when born SGA, OR 1.29 (95% CI 1.24-1.35). No increased risk was found after being born LGA.

Paper 3: The Apgar score is a resourceful marker of obstetrical care, as a substantial risk increase of needing education in special schools, OR =1.93(95% CI 1.75-2.14) low, or no grades when graduating from compulsory school, in nearly all school subjects, was found after being born with a 5 minute Apgar score under 7. One of 44 children born with an Apgar-score <7 at 5 minutes after birth will need education in a special school due to the factors leading to the low Apgar score.

Paper 4: A 50% decreased risk of an Apgar score<7 at 5 minutes was found in DM+GDM pregnancies after a planned CS in gestational week 38 as compared to planned vaginal birth (from gestational week 39 and beyond), ($p= 0.021$), but no decreased risk was found in the DM group ($p=0.08$), GDM group ($p=0.12$) or LGA group alone ($p=0.06$).

Paper 5: Offspring birth weight is a direct mirror of the maternal metabolic status, as a profound risk increase of developing both type 1 OR=3.46 (95% CI 3.12-3.83) or type 2 DM OR= 2.90 (95% CI 2.80-3.01) was found subsequent to giving birth to a LGA or macrosomic fetus.

Key words

Maternal diabetes, ductus venosus, nonmalformational cardiovascular disease, fetal programming, Apgar score, cesarean section, Large for gestational age, type 2 diabetes

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ABBREVIATIONS

ACOG	American College of Obstetrics and Gynecology
ADA	The American Diabetes Association
AGA	Appropriate for Gestational Age
ATC	Anatomic Therapeutic Chemical Classification
BMI	Body Mass Index
CI	Confidence Interval
CP	Cerebral Paresis
CRP	C-Reactive Protein
CS	Cesarean Section
CTG	Cardiotocography
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DV	Ductus Venosus
EP	Epilepsy
ER	Educational Registry
FECG	Fetal Electrocardiogram
GDM	Gestational Diabetes Mellitus
GLUT1	Placental Glucose Transporter
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
Hba1c	Glycosylated Hemoglobin
HDL	High-Density Lipoprotein
HIE	Hypoxic Ischemic Encephalopathy

ICAM-1	Intercellular Adhesion Molecule -1
ICD	International Classification of Disease
IGF-1	Insulin like Growth Factor-1
IPR	In-Patient Registry
IQ	Intelligence Quotient
IUGR	Intrauterine Growth Restriction
LDL	Low-Density-Lipoprotein
LGA	Large for Gestational Age
MBR	Medical Birth Registry
NDR	National Diabetes Registry
NMCVD	Non-Malformational Cardiovascular Disease
NNT	Numbers Needed to Treat
NO	Nitric Oxide
NP	Not Passed
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
P	Passed
PD	Passed With Distinction
PE	Passed With Excellence
pH	Hydrogen Ion Concentration
PI-DV	Pulsatility Index of the Ductus Venosus
PIV	Pulsatility Index of the Veins
PPV	Positive Predictive Value
PRS	Perinatal Revision South
S.D	Standard Deviation
SGA	Small for Gestational Age
SPDR	Swedish Prescribed Drug Register
TAMXV	Time Average Maximum Velocity

TNF-*A*	Tumor Necrosis Factor-Alpha
WHO	World Health Organization

BACKGROUND

Diabetes mellitus (DM) literally means “sweet urine” (Poretsky, 2009), and is a collective term for the many types of disease. As euphemistic as the description might seem, DM, in all of its forms, has detrimental health impacts on the pregnant mother and fetus. DM type 2 is a worldwide public health problem with a heaping global prevalence of 4.4% (366 million) in 2030 (Wild et al, 2004). Hence, the number of women with DM during pregnancy will also increase drastically.

Type 1 diabetes mellitus

In Sweden the prevalence of type 1 DM is approximately 0.5% of the population (40 000) and the peak incidence is between 5-14 years of age (National Board of Health, Diabetes, 2009 and 2010).Type 1 DM is an autoimmune disease, with the production of antibodies against insulin producing ß-cells in the pancreas (Eisenbarth et al, 1986), leading to an absolute deficit of insulin and therefore hyperglycemia.

Type 2 diabetes mellitus

In Sweden approximately 3-4% of the population has type 2 DM, most of whom are diagnosed after the age of 40. Few women have Type 2 DM before pregnancy, but the prevalence is on the rise mainly due to the increasing problem of obesity (Agardh et al, 2009). Type 2 DM and gestational diabetes mellitus (GDM) have similar pathogenesis (see below), and include hyperglycemia due to insulin resistance and relative insulin deficiency (Stumvoll et al, 2005). Moreover, hyperglycemia itself impairs pancreatic beta cell function and exacerbates insulin resistance, leading to a vicious cycle of hyperglycemia causing a worsening metabolic state. Type 2 DM is often accompanied by other conditions, including hypertension, high

serum low-density-lipoprotein (LDL) cholesterol concentrations, and low serum high-density-lipoprotein (HDL) cholesterol concentrations, which together with type 2 DM increases cardiovascular risk. This constellation of clinical conditions, together with central obesity, is referred to as the metabolic syndrome (DeFronzo et al, 1991).

Gestational diabetes mellitus

Defining gestational diabetes mellitus

The World Health Organization (WHO, 1999), American Diabetes Association (ADA, 2012), and American College of Obstetricians and Gynecologists (ACOG, 2001) have different strategies and cut-off levels for diagnosing GDM. In an attempt to illuminate the gray puddle of diagnosing GDM, approximately 25 000 women undertook a 75-g oral glucose-tolerance test (OGTT) (Metzger et al, Hyperglycemia and adverse pregnancy outcomes Study Cooperative Research Group, 2008) at 24 to 32 weeks of gestation, and a blinded assessment of neonatal outcome was performed. The primary outcomes were birth weight above the 90th percentile, caesarean section (CS), fetal hypoglycemia and cord blood serum C-peptide above the 90th percentile. No absolute glucose cut-off level for adverse outcome was found, adverse outcome (all primary outcomes) increased continuously with increased maternal blood glucose levels, as measured by the OGTT. Also the secondary outcomes reported (premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia) showed continuous linear associations with increasing OGTT values. The International Association of Diabetes in Pregnancy Study Groups has subsequently recommended new thresholds for diagnosing GDM and overt DM in pregnancy (Metzger, IADSPG Consensus Panel, 2010)(Table 1).

Table 1: New Diagnostic Criteria for Gestational Diabetes Mellitus

Proposed Diagnostic Thresholds		
Type of Glucose Test	Glucose Concentration Threshold	
	mmol/L	mg/dL
Gestational Diabetes Mellitus		
Fasting Plasma Glucose	5.1	92
1-h Plasma Glucose	10.0	180
2-h Plasma Glucose	8.5	153
Overt Diabetes in Pregnancy Fasting Plasma Glucose ≥7.0 mmol/L (≥126 mg/dL) HbA1c ≥6.5% Random Plasma Glucose ≥11.1 mmol/L (≥200 mg/dL) + confirmation		

Prevalence and pathophysiology

In Sweden the prevalence of GDM is approximately 2 % (Anderberg et al, 2007). Globally the prevalence varies between 7-17% depending on the population studied (Xiang et al, 2011). Also the diagnostic method used will influence the prevalence; an OGTT has been show to detect twice as many patients with GDM, than using random repeated glucose measurements (Anderberg et al, 2007).

Pregnancy can be seen as a metabolic stress test. In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, and maternal blood sugar levels are kept relatively constant or slightly lower fasting (Catalano et al, 1993 and 1999). During the later trimesters the demand for insulin is high, due to the placental release of several diabetic hormones; progesterone, human placental lactogen (HPL), human placental growth hormone, cortisol, prolactin, and tumor necrosis factor-alpha (TNF-α) (Homko et al, 2001) (Richardson et al, 2007). Women with GDM exhibit a chronic pancreatic beta cell deficit, even before pregnancy (Catalano et al, 1993 and 1999), and the pancreas cannot produce enough insulin to satisfy the increased tissue demand of insulin, leading to hyperglycemia. Obesity prior to pregnancy, and also weight gain during pregnancy, predisposes to GDM (Sibere et al, 2001).

CONSEQUENCES OF DIABETES DURING PREGNANCY

Effects on the mother

Short term maternal effects

Macrosomia, usually defined as a birth weight more than 4500 grams, (Ben-Haroush et al, 2004), is more common in diabetic pregnancies, and a risk factor for vaginal and fourth degree perineal tears (Eskander et al, 2009). Also, women with DM during pregnancy have an increased risk for preeclamsia and eclampsia (Montoro et al, 2005), of which a substantial portion is due to the increased rate of underlying chronic hypertension among diabetic women. Poor glycemic control, obesity, long duration of disease and pre-existing renal failure increases the risk of hypertensive complications. Women with type 1 DM in Sweden, have showed a 5 times higher risk of delivery with cesarean section, with its inherent risks such as wound infection, blood loss, and abnormal placentation in subsequent pregnancies (Deqlerq et al, 2007) (Simpson et al, 2001).

Long term maternal effects

The increased risk of developing type 2 DM after previous GDM is well established, and varies with the length of follow up time, with the reported incidence ranging from 2.6% to 70% (Kim et al, 2002) (Ben-Haroush et al, 2004)(Buchanan et al, 2012). As mentioned above the β-cell defect that typifies GDM is chronic (Buchanan et al, 1990), not acquired during pregnancy, and therefore could be the culprit of the high risk of type 2 DM in women with previous GDM (Buchanan et al, 2001 and 2005). Lauenborg et al, (2005) found a 3-fold increase of the metabolic syndrome in women with previous GDM, when compared to a population of 1000 age-

matched women from a population-based sample. Obese women with body mass index (BMI) > 30 kg/m^2 with previous GDM had a more than 7-fold increased prevalence of the metabolic syndrome, compared with normal-weight prior GDM women. However, it seems like not only obesity is the culprit leading to future type 2 DM, but perhaps an underlying pancreatic insufficiency among women with GDM, as the authors showed increased insulin resistance, measured as increased fasting serum insulin, in 87% of the obese women with previous GDM, vs. 61% in the obese control group.

Effects on the fetus

Short term effects on the fetus

Maternal DM during pregnancy is a high risk pregnancy (Persson et al, 1999) (Yang et al, 2006), and the list of adverse neonatal outcomes is long.

DM leads to an altered metabolic state with an increased supply of glucose and the anabolic hormone insulin. Maternal glucose and amino acid levels diffuse freely over the placenta (Rice et al, 1979), leading to fetal beta cell hyperplasia and increased fetal insulin levels. Insulin in itself is an anabolic hormone, stimulating fetal growth. The result is macrosomia, which complicates 30-50% of diabetic pregnancies (Persson et al, 2009) (Evers et al, 2002). Macrosomic fetuses to diabetic women exhibit an increased risk of birth injury and shoulder dystocia, fractures, and brachial plexus injury compared to macrosomic infants to women without DM (Yang et al, 2006)(Ecker et al, 1997) (Bryant et al, 1998) (Kolderup et al 1997). The increased risk is attributable to the increased fetal truncal obesity and larger shoulder diameter, and the risk of brachial plexus injury in macrosomic fetuses to diabetic women is approximated to 2-5% (Ecker et al, 1997). Macrosomia, per se, is a risk factor for neonatal morbidity and mortality, with the major cause of early neonatal death being birth asphyxia (Zhang et al, 2008).

Offspring to women with type 1 DM in Sweden, show more than 3 times increased risk of stillbirth, 2.5 times higher risk of major malformations and 3 times higher risk of very preterm birth (<32 gestational weeks) when compared to the non-diabetic population (Persson et al, 2009).

The incidence of congenital cardiac malformation in the offspring of diabetic mothers is considerably higher than the normal population, with

an incidence of 3-6%, (Wren et al, 2003) and include-double outlet right ventricle, truncus arteriosus, transposition of the great arteries, ventricular septal defect, and hypoplastic left heart syndrome (Wren et al, 2003)

Hypertrophic cardiomyopathy affects up to 40 % of newborn infants to type 1 DM mothers and is characterized by thickening of the interventricular septum (Garcia-Flores et al, 2011). Hypertrophic cardiomyopathy usually goes in regress in the neonatal period, but can in rare cases produce left ventricular outflow obstruction (Garcia-Flores et al, 2011). Myocardial thickening has even been observed in fetuses from mothers with well-controlled diabetic pregnancies (Jaeggi et al, 2001).

Furthermore, during the stress of birth, fetal electrocardiogram (ECG) changes have been described in fetuses to diabetic mothers (Yli et al, 2008). The changes in the ST interval of the fetal ECG were unrelated to asphyxia but rather explained as related to myocardial stress. This hypothesis is further supported in a recently published study where presence of ECG changes in fetuses to diabetic mothers were related both to higher proBNP levels in umbilical cord blood and ultrasound signs of cardiomyopathy neonatally. The concentration of umbilical cord blood proBNP was positively associated with the neonatal cardiac interventricular septal thickness and negatively associated with umbilical cord blood pH levels (Personal communication, Amer-Wåhlin).

To continue enumerating the dismal list of adverse outcomes, the risk of perinatal morbidity defined as low Apgar score, Erb palsy, and respiratory distress was shown approximately 3 times higher among offspring to type 1 diabetic Swedes in comparison to the non-diabetic population (Persson et al, 2009). Furthermore, newborns to diabetic mothers have an increased risk of hypoglycemia, hypocalcemia, hyperbilirubinemia, and polycythemia (Navneet et al, 2012).

Long term effects on the fetus

Fetal programming

According to the "fetal origins" hypothesis (Barker, 1989 and 1993), conditions, most likely nutritional, "program" the fetus for the development of chronic diseases in adulthood. This theory is based on epidemiological studies showing a correlation between low birth weight and later cardiovascular disease. The "thrifty phenotype" hypothesis postulates that poor fetal and early post-natal nutrition imposes metabolic adaptations to secure the fetus immediate survival. The result is reduced fetal growth. Conversely, these adaptations may lead to unfavorable effects in adult health, when fuel supply is ample (Barker, 1989).

During the plastic fetal period, environmental factors in utero, can switch genes "on" or "off". Hence, one genotype can give rise to a range of phenotypes. This is referred to as epigenic modification and is thought to be the basis of the programming phenomenon (Gluckman et al, 2005). It is not difficult to comprehend the importance of the prenatal environment, as essential growth and development is completed before birth, with over 75% of one's lifetime's cell divisions occurring in utero (Yajnik, 2006). The long term consequences of an environmental event are also dependent if it coincides with a critical period of rapid cell proliferation in the fetus (Symonds et al, 2009). Maternal under nutrition during late gestation, during which period the fetus grows rapidly, has showed to have a larger impact on fetal birth weight than malnutrition during early gestation (Roseboom et al, 2001).

Fetal exposure to maternal DM is associated with offspring adult adiposity (Lawlor et al, 2011), later type 2 DM (Clausen et al, 2009), hypertension (Clausen et al, 2008)(Huxley et al, 2000) and dyslipidemia (Boney et al, 2005). It is not clear if this is due to fetal programming or to an earlier onset of obesity, which is common among children of diabetic mothers. However, children to mothers with GDM and type 2 DM during pregnancy have shown higher blood pressure than children born to mothers developing type 2 DM after pregnancy. Since both groups have a genetic predisposition to DM, this could imply that the risk of cardiovascular disease is set at much earlier date, perhaps as a consequence of the intrauterine environment (Bunt et al, 2005). Also supporting the fetal programming theory are the extensive studies regarding intrauterine exposure to diabetes performed on the Pima Indians, showing how maternal diabetes in utero was the strongest single risk factor for obesity in

Pima Indian children, independently of maternal obesity and birth weight (Pettitt et al, 1983 and 1987) (Dabelea et al, 2001).

Mechanism behind the impact of maternal diabetes on fetal health

The pathological pathway from exposure of intrauterine DM to both short and long term disease are not fully mapped out, but include altered glucose and lipid metabolism in the offspring, placental aberrations, increased oxidative stress, immune system modulation and endothelial dysfunction, all described below (Soulimane-Mokhtari et al, 2005) (Baynes et al, 1999) (Dahlgren et al, 2001) (Dandona et al, 2004).

Hyperinsulinemia stimulates, not only glucose uptake, but also increased fat synthesis and therefore an increase in body size. Macrosomic and obese offspring of diabetic rats exhibit high adipose tissue weight, together with high adipose tissue lipid contents (Soulimane-Mokhtari et al, 2005), and they show high serum and liver lipid levels (Khan et al, 2006)(Merzouk et al, 2001). Maternal hypercholesterolemia during pregnancy is also associated with increased fatty streak formation in fetal arteries and accelerated progression of atherosclerosis during childhood in the offspring (Palinski et al, 2002). Manderson et al (2002) found differences in metabolic, cardiovascular and inflammatory variables in the offspring of type 1 diabetic mothers, aged 5 to 11 years old, when compared to offspring of non-diabetic mothers. The mean serum IGF-1, total cholesterol and cholesterol-to-HDL ratio were statistically higher in the offspring of diabetic infants than in the control offspring.

Oxidative stress, endothelial dysfunction and immune system modulation

Put simple, endothelial dysfunction is the inability of the arteries to dilate when stimulated by vasodilators, such as nitric oxide (NO). The NO diffuses from the endothelium to the underlying layer of vascular smooth muscle cells and leads to vasodilation. In pregnancies complicated by GDM (Westermeier et al, 2009), intrauterine growth restriction (IUGR) (Casanello et al, 2007) or preeclampsia (Escudero et al, 2008), the synthesis and/or bioavailability of NO are altered leading to changes in blood flow of the placenta (Myatt et al, 2010). In the placenta and the distal segment of the umbilical cord (Fox et al, 1990), vascular tone is regulated by the synthesis and release of vasoconstrictors and vasodilators from the endothelium (Myatt et al, 2010). The reduced ability of this tissue to stimulate NO-mediated vasodilatation is referred to as endothelial

dysfunction (Deanfield et al, 2005). This phenomenon is strongly correlated with cardiovascular disease (CVD) risk factors (Wierzbicki et al, 2004) and with early states of chronic diseases such as hypertension (Versari et al, 2009), hypercholesterolemia (Libby et al, 2011), DM (Avogaro et al, 2006), hyperhomocysteinaemia (Cheng et al, 2009), and chronic renal (Nakagawa et al, 2011) and cardiac failure (Enomoto et al, 2011).

Both DM and macrosomia are associated with increased oxidative stress (Baynes et al, 1999). High blood glucose levels induce oxidative stress which, in turn, induces the production of highly reactive toxic oxygen radicals, which destroy the lipid bilayer in the plasma membranes (Kamath et al, 1998). Both the newborn and mother with GDM have showed increased oxidative stress manifested as increased lipid peroxidation and protein oxidative damage in the erythrocytes, which in turn leads to an increased risk of developing platelet hyper-aggregability in the fetus (Kamath et al, 1998).

Maternal type 1 DM is also associated with significant increase in the cord blood markers of inflammation and endothelial dysfunction, ICAM-1 and CRP (Nelson et al, 2007). Low-grade inflammation has previously been reported to be a link between insulin resistance, obesity, and type 2 DM in adults (Dandona et al, 2004). In an animal model, Dahlgren et al, (2001) showed how intrauterine exposure to cytokines (interleukin IL-6) were associated with increased fat mass and insulin resistance later in life. A high inflammatory burden, oxidative stress and glucotoxicity give rise to endothelial dysfunction in fetal vessels, possibly resulting in a direct increased susceptibility for future cardiovascular disease. Altered function of the placental vessels might also dysregulate blood and nutrient supply to the fetus, potentially stimulating fetal programming.

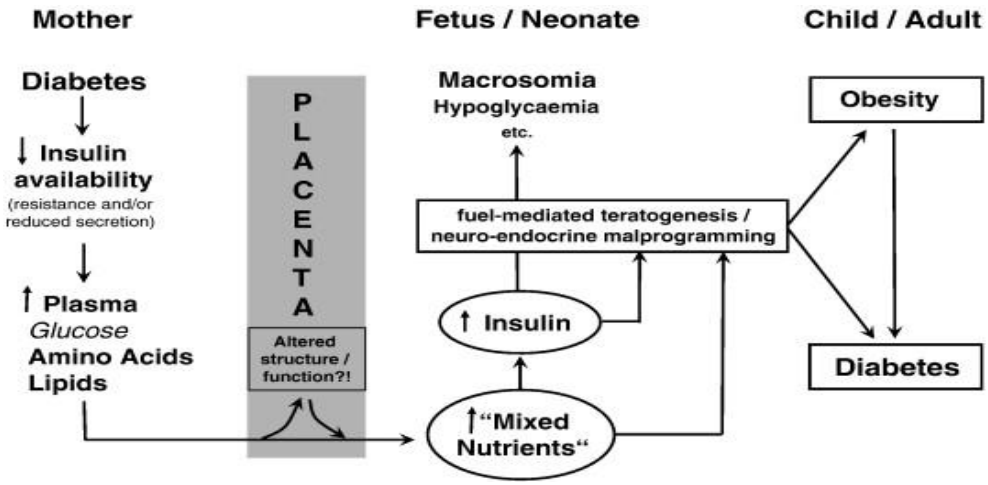
Influence on the Placenta

Another possible mechanism leading to adverse outcome, such as macrosomia, after intrauterine exposure to DM, is an altered capacity of the diabetic placenta to transport nutrients. Gaither et al, (1999) showed increased expression of the placental glucose transporter GLUT1, in type 1 DM, which might lead to increased nutrient supply even during euglycemia. The highest risk of hypoglycemia is during the first trimester (Evers et al, 2002), the same time during which the placental structures are formed, and the placenta is more sensitive to modifications. Weiss et al, (2001) showed how in vitro hyperglycemia inhibited trophoblast proliferation which delays

placental growth and development. This might explain the higher incidence of spontaneous abortion, preeclampsia and IUGR associated with DM.

Fetal insulin response is dependent on the duration and pattern of hyperglycemia, mild chronic hyperglycemia in combination with 3 marked hyperglycemic spikes per day stimulated fetal insulin secretion more than chronic and more severe hyperglycemia or hypoglycemia (Carver et al, 1996). In a mouse model, Ericsson et al (2007), administered intravenous glucose injections in early and late gestation, and showed how modest repetitive elevation of maternal blood glucose in early pregnancy altered fetal growth, presumably due to increased placental growth and up regulation of placental nutrient transport capacity. In contrast, a single glucose injection early in gestation or 3 injections late in pregnancy did not alter fetal growth.

Figure 1. A schematic summary of maternal DM and fetal programming. Figure reprinted after permission from Elsevier (Plagemann et al 2011).



OBSTETRICAL MANAGEMENT OF THE DIABETIC PREGNANCY

In Sweden, specified programs exist, in order to provide optimal health care to the diabetic pregnant women. These include teams with obstetricians, endocrinologists, midwifes, nurses specialized in DM, and nutritionists. Pregnancies complicated by type 1, type 2 and GDM are monitored similarly. Management includes monitoring blood sugar, education regarding caloric intake, and physical activity. If glucose goals are not met, or in cases with accelerated fetal growth, insulin treatment is recommended. For women with GDM, postpartum screening for maternal type 2 DM is recommended (ACOG, 2009).

The aim with glucose monitoring during pregnancy is to keep maternal HbA_{1c} as near normal values as possible. However, even in cases with good maternal metabolic status, as measured by HbA1c, adverse outcome such as macrosomia (Evers et al, 2002) and septal hypertrophy (Jaeggi et al, 2001) occur. HbA_{1c} decreases in normal pregnancies due to increased turnover of maternal erythrocytes and lower fasting blood sugar and thus might not be an optimal marker for metabolic control during pregnancy (Lurie and Danon, 1992). A Danish study, demonstrated a continuous decrease of HbA_{1c} during pregnancy in non-diabetic pregnant women, compared to non-pregnant women (Nielsen et al, 2004). Elliot et al, (2000) showed falling HbA_{1c} values with advancing gestational age despite relatively unchanged blood glucose levels over the same time period. Fluctuations in maternal glucose levels might explain accelerated fetal growth better than HbA_{1c} values, which reflect average glucose levels over a 4-6 week period (Greco et al, 2003). Also, the increased rates of macrosomia despite near normal HbA_{1c} levels could be the result of rebound hyperglycemia caused by hypoglycemia.

The down side of a tight metabolic control is the increased risk of hypoglycemia. HbA_{1c} does not measure the variations of blood glucose, and

therefore gives no information of maternal and fetal hypoglycemia. It has been suggested that frequent episodes of hypoglycemia in cases with normal HbA_{1c} might indicate that a large proportion of the blood sugar values could be in the hyperglycemic range; with hypo and hyperglycemic values masking each other (ter Braak et al, 2002). Not only could hyperglycemia be the culprit behind adverse outcome in insulin dependent diabetic pregnancies, also the adverse effects after a hypoglycemic insult. Animal studies clearly indicate that hypoglycemia is potentially teratogenic during organogenesis (Smoak et al, 1997) (Tanigawa et al, 1991). Children subject to neonatal hypoglycemia have shown lower scorings in test for minimal brain dysfunction than controls and were also more often reported to be hyperactive, impulsive, and easily distracted (Stenninger et al, 1998). It is therefore plausible that recurrent or severe maternal hypoglycemic episodes might affect the neurodevelopment of the fetus.

Fetal surveillance

All women are offered free antenatal care in Sweden, and this includes an ultrasound around gestational week 18 in order to, among other things, detect congenital malformations.

Later in gestation, fetal surveillance is conducted to answer two main questions; When should we deliver? And how should we deliver? The Fifth International Workshop-Conference on GDM (Conway et al, 1998)(Metzger et al, 2007), recommend in all types of DM:

- Fetal growth should be assessed by ultrasound, usually every other week starting at gestational week 32. Biophysical profile testing and Doppler velocimetry to assess umbilical blood flow "may be considered" in cases of excessive or poor fetal growth, or when there are comorbid conditions, such as preeclampsia.
- Fetal heart rate registration with cardiotocography (CTG) should be "considered" after 32 weeks' gestation in women on insulin and "at or near" term in women requiring only dietary management.
- Mothers with DM should be taught to monitor fetal movements during the last 8–10 weeks of pregnancy and to report immediately any reduction in the perception of fetal movements.

Obstetrical ultrasound and Doppler blood flow assessment

Fetal weight estimate

Fetal weight is assessed by ultrasound, usually starting at gestational week 32. The incidence of fetal macrosomia in DM-pregnancies ranges from 30-50% (Persson et al, 2009) (Evers et al, 2002) compared to 3.6% in the general population. Fetal macrosomia has been defined in several different ways, including birth weight of 4000-4500 g or greater than 90% for gestational age (Ben-Harousch et al, 2004)(Chauhan et al, 2005). The terms small, appropriate and large for gestational age (SGA, AGA, LGA) are statistical terms defining fetal weight deviation in relation to the standard population weigh curves. Infants with a birth weight less than 2 standard deviations (SD) below the expected weight for gestational age are classified as SGA, whereas infants exceeding 2 SD above expected weight for gestational age are classified as LGA (Marsal et al, 1996).

A problem detecting the LGA fetus, however, is the low sensitivity of current sonographic methods (Ben Haroush et al, 2004). Commonly used weight formulas are associated with very large deviations when used trying to identify the macrosomic fetus. False diagnosis of macrosomia, has been shown to increase the risk of CS 2.5 times, regardless of actual birth weight. Failure to detect macrosomia was associated with higher rates of perineal trauma, 5-minute Apgar scores less than 7, and neonatal trauma, mostly related to the higher rate of surgical vaginal deliveries (Melamed et al, 2010). Chauhan et al, (2005) reviewed 20 articles that calculated the sensitivity and specificity of sonographic estimated fetal weight of >4000 g to accurately identify a macrosomic fetus. Among diabetic patients the detection rate of 60% to identify newborn weighing >4000 g, was somewhat higher than in a non-diabetic population. Attempts for formulas for more accurate estimation of fetal weight are in the pipeline and include both two and three dimensional ultrasound (Lindell et al, 2012). However, not only are there difficulties when estimating the weight of large fetuses, buy also maternal obesity, common among women with GDM, increases the risk of erroneous ultrasound measurements (Simic et al, 2010).

Doppler blood flow assessment

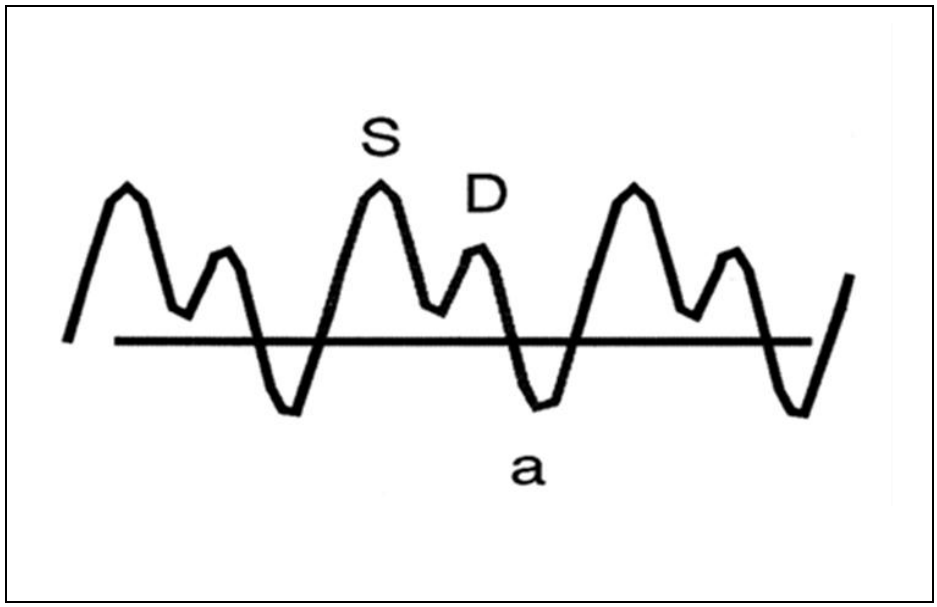
Doppler blood flow measurements in the umbilical artery are used in high risk pregnancies complicated by IUGR, preeclampsia or DM. Fetuses with IUGR and hypoxia have demonstrated increased resistance to flow in the umbilical arteries and redistribution in the fetal circulation with reduced resistance and increased velocity in the internal carotid and middle cerebral

artery (Groenenberg et al, 1989)(Vyas et al, 1990). The redistribution of blood flow to vital organs such as brain, heart and adrenal glands, in fetuses exposed to chronic hypoxia, is referred as “the brain sparing” effect (Vyas et al, 1990).

During ventricular systole (S), the highest pressure gradient between the venous vessels and the right atrium occur, resulting in the highest blood flow velocity towards the fetal heart. The second peak of forward flow is seen in early diastole (D) in conjunction with the opening of the atrioventricular valves and passive early filling of the ventricles. During late diastole the atrium contracts (a), giving the lowest flow velocity in the cardiac cycle. During atrial contraction, the foramen ovale closes preventing blood flow from the ductus venosus (DV) to the left atrium (Hecher et al, 1996).

The venous pulsatility index (PIV), is obtained according to following PIV= (S-a)/TAMXV. S indicates peak systolic velocity; D, peak diastolic velocity; a, peak reverse velocity or nadir during atrial contraction; and TAMXV, time average maximum velocity. (Hecher et al, 1995)

Figure 2. Venous waveform



Ductus venosus blood flow assessement

The DV play a major role in venous return flow to the fetal heart. Well-oxygenated blood from the placenta flows through the DV to the foramen ovale and the left atrium (Edelstone et al, 1978). Approximately 20-30% of the venous blood from the placenta by-passes the liver, and goes directly to the fetal heart (Kiserud et al, 2000) (Bilotti et al, 2000). The DV functions as a shunt, and in cases of hypoxia the DV dilates and therefore increases the percentage of well-oxygenated blood flowing from the placenta to the fetal heart. When the DV dilates, the flow in diastole will decrease, and pulsations in the umbilical vein can be detectable. When the DV is entirely dilated, back flow will be seen in late diastole (a-wave)(Kiserud et al, 2000).

Blood flow alternations in the DV has been postulated to reflect cardiac function (Kessler al, 2006). Abnormal DV flow patterns have been associated with congenital cardiac defects (Bilardo et al, 2001), increased heart failure markers (Girsen et al, 2007 and 2008), myocardial hyperthrophy in diabetic pregnancies (Zielinsky et al, 2004), and found higher in fetuses with congenital heart disease that died than those who survived (Baez et al, 2005).

Increased values of the pulsatility index for veins (PIV) and absent or reversed flow during atrial contraction, in the DV, have been correlated with adverse pregnancy outcomes (Bilardo et al, 2004). Data is contradictory concerning the benefit of analyzing PI-DV to predict adverse neonatal outcome in IUGR fetuses. In a study with 70 IUGR fetuses, a PI-DV value above 2 SD at 2–7 days before delivery discovered a three-fold increase of adverse outcome, and when the DV PIV rose above 3 SD on the day preceding delivery, the chance for adverse neonatal outcome was increased 11-fold (Bilardo et al, 2004). However, Ritter et al (2004) found no correlation, in a study including 42 IUGR fetuses, between increased PI-DV and fetal outcome before 32 gestational weeks, even in cases of severe growth restriction based on placental insufficiency. In an unselected collective of 87 high-risk pregnancies (IUGR, pre-eclampsia, DM) Hofstaetter et al, (1996) found no correlation between pathologic flow patterns in the DV and fetal outcome. Also, in diabetic pregnancies the benefit of analyzing PI-DV to predict adverse neonatal outcome is sparse. In pregestational DM pregnancies, the sensitivity of an abnormal peak velocity index of the DV (+ 2 S. D) in predicting adverse perinatal outcomes was 53.3%, the specificity was 74.6%, the positive predictive value was 32.0% and the negative predictive value was 87.7% (Wong et al, 2010).

Timing and route of delivery

The literature (Boulvain et al, 2001) (Witkop et al, 2009) (Lurie, 1992 and 1996) (Kjos et al, 1993)(Peled et al, 2004) (Conway et al, 1998) regarding the optimum route and timing of delivery in diabetic pregnancies leaves many questions unanswered. When abnormalities in fetal growth is suspected, or in cases of other complicating factors, intervention in the form of induction or elective CS can be performed. Practice guidelines published by ACOG recommend considering a planned CS if the estimated fetal weight exceeds 5 000g in women without DM and 4 500 g in women

with DM (Sokol et al, 2003). The ADA recommends delivery during the 38th week unless obstetric considerations dictate alternative management (ADA, 2004).

Delivery by CS is substantially increased in both patients with type 1 DM (Shand et al, 2008) and GDM, particularly in overweight patients (Ehrenberg et al, 2004). A large retrospective cohort study of 28,863 nulliparous term singleton vertex births showed that 38% of diabetics were delivered by CS (Coonrod et al, 2008). In a Danish prospective study with 1,218 type 1 diabetic mothers, as many as 56% were delivered by CS, and of these, 55% were performed electively (Jensen et al, 2004).

The cons of an elective CS are mainly maternal, including increased risks for infection, postpartum bleeding, deep venous thrombosis, and cumulative risk of repeated CS in following pregnancies with increased risk of uterine rupture and abnormal placentation (Deqlerq et al, 2007) (Simpson et al, 2001). The increased maternal morbidity must be carefully weighed against the fetal benefits, but also potential fetal cons of an elective CS. The benefits include lower risk of dystocia, birth injury and perhaps asphyxia, especially in the case of a macrosomic fetus (Zhang et al, 2008).

The rates of stillbirth in diabetic pregnancies are higher than the background population, but fortunately still low, making it difficult to analyze death as an endpoint in randomized trials assessing mode and timing of delivery. A Cochrane review concludes that there is very little evidence to support either elective delivery or expectant management at term in pregnant women with insulin-requiring DM (Boulvain et al, 2001). Only one randomized controlled study has compared elective induction versus expectant management in insulin-requiring diabetic pregnant women at term (n=200). The risk of macrosomia, defined as birth weight above 4 000 g, was reduced in the active induction group, no significant difference was found in CS rates, shoulder dystocia, neonatal hypoglycemia or perinatal deaths (Kjos et al, 1993). Another systematic Cochrane review (Witkop et al, 2009) analyzed the above study (Kjos, 1993) and 4 observational (Lurie, 1992 and 1996) (Peled et al, 2004) (Conway et al, 1998) studies. Due to inherent flaws in the studies, no robust conclusions could be made. A careful summary of the review (Witkop et al, 2009) read out a reduction in macrosomia and shoulder dystocia with labor induction and cesarean delivery at 38 weeks of gestation. Conway et al, (1998) studied 2 604 diabetic women undergoing ultrasonographic fetal weight estimates during the 37th and 38th week of gestation. If the estimated fetal weight was above or equal to 4 250 grams the patient underwent an elective CS and if

the estimated fetal weight was over or equal to the 90th percentile but under 4 250 grams the patient underwent induction of labor. Fewer infants were macrosomic and the incidence of shoulder dystocia was lower in the group undergoing elective CS or labor induction than in the expectant management group (Conway et al, 1998).

Outcome measurement

After monitoring the diabetic pregnancy, measuring what can be measured, and finally delivering the baby, a question remains still unanswered. How well did we do it? How can we evaluate obstetrical care?

There are several challenges in measuring quality in obstetrical care. The used outcome measures commonly used are the Apgar score, arterial and venous cord blood acid base status, neonatal morbidities and perinatal mortality. The incidences of hard end point measurements, such as perinatal mortality as well as asphyxia, are rare. The coverage in national registries of outcome data, e. g arterial and venous cord blood sampling, is not satisfactory and furthermore no definite correlation between acidosis at birth and long term neurological outcome seems to exist (Mittendorf et al, 2008)(Pschirrer et al, 2000). Difficulties also exist deciding if the hypoxic insult happened before or during labor. An easy, low cost, outcome measure that is used globally is the Apgar score.

The Apgar score

The Apgar score was coined by the anesthesiologist Virginia Apgar (Apgar, 1952) in order to quickly evaluate the need and success of neonatal resuscitation. At 1, 5 and 10 minutes after birth, the newborn is clinically evaluated and scored (0-2 points) regarding heart rate, respiratory effort, muscle tone, reflex irritability, and color. For each evaluation, a maximum of 10 points can be given. An Apgar score of 0 to 3 after 5 minutes is one of the suggested criteria for an intrapartum asphyxial insult (ACOG, Task Force on Neonatal Encephalopathy and Cerebral Palsy, 1992). However, a number of factors may give a low Apgar score, such as drugs, trauma, congenital anomalies, infections, hypoxia, hypovolemia, and preterm birth (Freeman et al, 1988). Given this, a low Apgar score cannot be used alone to establish the diagnosis of asphyxia.

Although the predictive value of adverse neonatal outcome after a low Apgar score has been questioned, an Apgar score below 7 at five minutes after birth has been associated with an increased risk for cerebral paresis (CP), epilepsy (EP), and mental retardation (Thorngren-Jerneck et al, 2001)(Moster et al, 2001) (Lie et al, 2010). Recent studies have also shown an association between low 5 minute Apgar scores and reduced scoring on intelligence quotient (IQ) tests in male draftees in Sweden and Denmark (Ehrenstein et al, 2009) (Odd et al, 2008).

AIMS OF THE STUDIES

Paper 1

To investigate if pulsatility index of the ductus venosus (PI-DV) was affected in fetuses to diabetic mothers, in an attempt to assess short term cardiac impact.

Paper 2

To investigate if offspring exposed to intrauterine diabetes, had an increased risk of cardiovascular disease as adults, as measured by consumption of drugs for cardiovascular disease.

Paper 3

To evaluate if the 5-minute Apgar score can be used as an outcome marker for obstetrical care, by investigating the relation between 5-minute Apgar scores and school performance at 16 years of age.

Paper 4

To investigate fetal outcome, as measured by 5-minute Apgar scores, in relation to mode of delivery in diabetic pregnancies.

Paper 5

To investigate if fetal birth weight could be used as a proxy to mirror the maternal metabolic status, by investigating the mother's future risk of DM in relation to offspring birth weight.

MATERIAL AND METHODS – GENERAL COMMENTS

All of the following studies were approved by the Ethics Committee, Lund's University, Sweden.

Registers used

The following registries were represented in one or more of the papers. All of the following registries can be linked to each other via each person's unique personal identity number (PIN).

The Medical Birth Registry

The Medical Birth Registry (MBR) (Källén et al, 2003), held by the Swedish National Board of Health, started in 1973 and contains medical information on 99% of all births in Sweden. All women in Sweden are offered free antenatal, delivery and pediatric care. Standardized record forms are used in all antenatal clinics, all delivery units, and for all pediatric examinations during the child's first month of life. Before 2008, all data were inserted manually and sent to Statistics Sweden. Since 2008, an increasing part of all obstetric units send their data electronically, directly from the patients' medical records.

The register includes, among other things, details of each individual´s previous pregnancies, which delivery ward she gave birth, gestational age, mode of delivery, diagnoses of both the mother and child (registered according to International Classification of Disease (ICD) –codes), surgery-codes, pain management, child's sex, weight, length and head circumference at birth. Information regarding two important potential confounders, maternal BMI and smoking, was first available from 1983.

As with all large registers, there is invalid and missing data the MBR. Missing data will affect all estimates of prevalence, but will usually have little impact on risk estimates if the lack of information is random. A quality report has been made (Källén et al, 2003), in which data from 500 patients in the MBR was compared to the information found in the original medical records. The loss of information is estimated at between 0.5 and 3 percent a year, and is slightly higher for children who are stillborn. Regarding correct coding for elective and emergency CS (used in paper 4), the research report stated that the register information is reasonably adequate at term deliveries, but that the frequency of elective sections at preterm deliveries is grossly overestimated. Information on birth weight is lacking for 0.32 per cent of all infants, and the vast majority of weights were correct.

The Perinatal Revision South Registry

The Perinatal Revision South Registry (PRS) is regional quality assessment registry, which started in 1994, with obstetrical and neonatal data from delivery wards in the Southern district of Sweden. The variable content of the PRS is to some extent similar to that of the MBR. The most important difference is that the PRS contains detailed neonatal data reported directly from the neonatal units and also information on blood gases at birth and duration of delivery.

The Swedish Prescribed Drug Registry

Since 2005, data on all dispensed and prescribed drugs in Sweden are available in the Swedish Prescribed Drug Register (SPDR), also held by the Swedish National Board of Health (Swedish registry of prescribed and dispensed drugs 2005-2010 National Board of Health: 2010). Information regarding type of drug, amount, price and expedition date, are available. Via the individuals PIN, information regarding gender, age, but also registered residence can be found. Pharmaceutical consumption is classified according to the Anatomic Therapeutic Chemical Classification (ATC). In the SPDR, the loss of PIN-codes is approximately 0.3%.

The Swedish In-Patient Registry

The IPR (Inpatient diseases in Sweden, National Board of Health, 2010) holds data on patients admitted to all Swedish hospitals since 1987; date of admission, date of discharge and diagnoses registered for each admission. More than 99% of all somatic hospital discharges are registered in the IPR. The positive predictive value (PPV) for diagnoses in the registry is generally 85-95% (Ludvigsson et al, 2011).

The National Diabetes Registry

The NDR is a national diabetes registry that started in 1996, and contains medical information regarding, but not restricted to, type of DM, year of diagnosis, metabolic status and treatment. Approximately 60% of the newly diagnosed patients with DM were registered in the NDR in 2008, and 80% in 2010. Information is collected from both primary care units and hospital units (National Diabetes Register, 2010).

The Educational Registry

The Swedish Educational Registry (ER) is held by the Swedish National Board of Health, and contains information regarding the highest educational level of all Swedish residents between the ages 16-74 years of age. An evaluation of the register has shown that the highest educational level is unknown for approximately 2% of the population. Higher frequencies of invalid or missing data are found the lower educational level the person has, or among persons born abroad (Statistics Sweden, Background Facts, and Evaluation of the Swedish Register of Education).

ICD-codes for DM (paper 1-2, 4-5)

In the MBR, ICD code-8 was used from 1969-1986, ICD-9 from 1987, and ICD-10 from 1997 (from 1998 in the southern part of Sweden). ICD-codes for GDM were first available 1987.

ICD-codes for pre-existing insulin dependent DM are; ICD8- code: 250, ICD-9: 250 and 6480, and ICD-10: O24.0.

The ICD-codes for DM complicating pregnancy, childbirth or the puerperium (GDM) are ICD-9 code: 648.8 and ICD- 10 code: 0.24.4.

Ultrasound measurement techniques

Ultrasonic assessment of estimated fetal weight and birth weight was evaluated in accordance with the Swedish national fetal weight-based growth standard (Marsal et al, 1996). Infants with a birth weight less than 2 SD below the expected weight for gestational age were classified as SGA, +/-2 S. D were classified as AGA, and infants exceeding 2 SD above expected weight for gestational age were classified as LGA.

Doppler blood flow assessment

Doppler velocimetry was performed with one of the following ultrasound systems (Paper 1): Aspen Acuson System (Acuson, Mountain View, CA), Acuson Sequoia 512 (Acuson, Mountain View, CA), Philips HDI 5000 System (Philips Medical Systems, Bothell, WA), Voluson Expert 730 Ultrasound System (GE Kretztechnik, Zipf, Austria). The examinations were done by experienced sonographers, at Lund and Malmö University hospitals, transabdominally using transducers with ultrasound frequency 2-7 MHz and with the lowest setting of high-pass filter (always <125 Hz). The recordings of DV blood velocity were done in the transverse section of fetal body; the angle between the ultrasound beam and the direction of the DV blood flow was kept below 45^{o}. The umbilical artery blood velocities were recorded from the mid-portion of the umbilical cord. At least 5 uniform heart cycles were used for calculation of PI in the Doppler shift spectrum records obtained from the DV and umbilical artery during periods without fetal breathing movements or general movements.

The umbilical artery blood flow patterns were classified according to semiquantitative blood flow classes (BFC) (Gudmundsson et al 1991):

Table 2. Blood flow classes

BFC	Pulsatility index	Direction of flow
Normal BFC	Normal umbilical artery PI	Positive diastolic flow
BFC I	PI >mean+2 SD <mean+3 SD	Positive diastolic flow
BFC II	PI >mean+3 SD	Positive diastolic flow
BFC IIIA		Absent diastolic flow
BFC IIIB		Reverse diastolic flow

Statistics

Power analysis

In the ideal world a study would commence with the calculation of how many subjects would be needed in order to have a fair chance to detect an association if it truly exists, and then design the study. In many situations, including in our studies, the available subjects are already known, and power calculations were performed to calculate the minimum effect size that was likely to be detected, and thus if the study was worth performing. If a study has too small sample size, a statistically negative result is not conclusive and doesn't rule out a true association between exposure and disease. In addition to the sample size, study power (commonly set at 80% probability to find a true association) is determined by the significance level (α), the probability of type II error (ß), and the standard deviation of data. Significance level is usually set at $p= 0.05$. If the test has a $p < 0.05$, the null hypothesis is rejected (see null hypothesis below). A type II error is when the null hypothesis cannot be rejected ($p>0.05$), even though the null hypothesis in reality is false. In cases of a type II error, the study gives a false negative result (Hennekens et al, 1987).

Testing the null hypothesis

Statistical tests, used in our studies for hypothesis testing between two groups are Fishers exact t-test and Wilcoxon rank sum test. These tests are used in order to reject the null hypothesis, which conservatively might state: no difference between the two groups; no effect of the treatment; no change over time. A predefined level of significance is decided, usually $p< 0.05$. When $p<0.05$, the null hypothesis can be rejected.

Confidence Intervals

Data in our studies were expressed as Odds Ratios (OR) with 95% Confidence Intervals (CI) (Miettinen, 1974). While a p-value gives an answer how compatible the results are with the null hypothesis, the OR with CI gives us information of the size of the difference between the two groups, and also information about the uncertainty of the estimate. A 95% CI gives an estimated range of values which is 95% likely to include the parameter studied (e.g. estimate of OR for low school grades). The estimated range is calculated from the given set of sample data (Hennekens et al, 1987). The width of the CI gives us some idea about how uncertain we are about the unknown parameter. A very wide interval may indicate a large uncertainly, or perhaps more data should be collected before anything very definite can be said about the parameter.

Confidence intervals can be more informative than the simple results of hypothesis tests (where “reject the null hypothesis “ or “don’t reject the null hypothesis” is decided) since they provide a range of plausible values for the unknown parameter.

Confounding

A confounding factor is defined as a factor that is associated with both the exposure and the outcome studied, independently of each other. Confounding can lead to both false negative and false positive associations. Classical confounders in perinatal epidemiology are gender, age, smoking, and weight. An example would be if the association between Downs’s syndrome and residential area was investigated. Age would be a typical confounder as it affects both exposure (which areas people live) and outcome (Downs’s syndrome). There are different ways to avoid con-

founding factors, both during the design or analyzing phase of a study. During the design phase confounders can be avoided by randomization, by limiting the study population to exclude cases with the confounding factor (e.g., by only including non-smokers), or matching so confounders are evenly distributed among both cases and controls.

Analytical methods and tests

Mantel Haenzel and multiple logistic regression

In our studies, confounding was controlled in the analyzing phase of the studies, by either stratifying for the confounding factors according to the Mantel Haenzel procedure (1959), or performing a multiple logistic regression. To simplify, stratifying according to Mantel Haenzel was performed in the studies with large study populations. In the cases of small populations or few controls a multiple logistic regression was performed (Paper 4). When performing a multiple logistic analysis, it is possible to control for multiple confounders simultaneously when analyzing the association between an exposure and outcome.

A multiple linear regression or multiple logistic regression can be performed, depending on how data presents itself. Multiple linear regression can be used when the outcome variable is continuous. In cases of binary outcome variables (yes/no, alive/dead) multiple logistic regression is more appropriate. While performing a linear logistic regression, it is assumed that a log linear association exists between the variable studied and the outcome (e.g. age and times being married). But in many situations the association can be U-formed rather than linear, (e.g. alcohol consumption and risk of cardiovascular disease). Different statistical techniques can test the adequacy of a linear fit. If the association is curved, then a polynomial logistic regression, rather than linear, should be performed. This could easily be achieved by, e.g., adding a second degree of the variable in question to the model.

When performing a multiple logistic regression first a univariate analysis is performed to insure that each variable put in the multiple model is, in fact, a confounder. In the univariate model a Hosmer-Lemoshov (Hosmer DW, Lemeshow S, 1989) , “The goodness of fit “ test, is performed to investigate how the association between the confounder and exposure/outcome is best

described. That is, is the correlation linear, squared, or best described in classes? The goodness of fit (Hosmer-Lemoshov test), measures how well the model describes the outcome variable, by investigating how close values predicted by the model are to the observed values (Bewick et al, 2005). If p was < 0.20 for the plausible confounder in the univariate analysis, it was entered in the multiple logistic model. The final multiple model consisted of at least 10 times more cases than variables analyzed.

Fisher's exact test

Fisher's exact test is a significance test which can be used in cases with small sample sizes, measuring the association between two variables in a 2x2 contingency table.

Wilcoxon rank sum test

Wilcoxon rank sum test is a non-parametric test which is used to investigate whether the values of a certain variable tend to be higher in one of two study groups. The Wilcoxon rank sum test could be used irrespective of distribution or sample size. Wilcoxon rank sum test is used for continuous variables.

Cox analysis

The risk of developing CP or EP (paper 4) depending on mode of delivery (planned vaginal or elective CS) was expressed as a hazard ratio, using a Cox regression model. The final Cox regression model was created as described for the multiple logistic regression model. The hazard function is the probability of the development of the above mentioned diseases during a certain time interval, divided by the whole time interval, in children without disease at the start of the time interval. The date of the study exit was set to the date of the first diagnosis of CP or EP, the date of death, or the date of the data retrieval (December 31, 2009), depending on which event happened first.

Kaplan Meier analysis

Kaplan Meier analysis is commonly used to produce survival curves, perhaps after a certain treatment or after a diagnosis of a disease.

In our study, (paper 5), Kaplan Meier estimates were used to show the prevalence of future maternal DM, over time, depending on fetal birth weight classification.

MATERIAL AND METHODS SPECIFIED, PAPER 1-5

Paper 1

Fetal blood flow parameters of women with preexisting insulin dependent DM (Group DM; n=86) and women with DM arising in pregnancy (Group GDM; n=56) were collected retrospectively from the clinical databases of the Departments of Obstetrics and Gynecology in Lund and Malmö, 1998-2007. Only the blood flow data from the last examination before delivery were included in the study.

Clinical data regarding maternal DM and neonatal outcome were obtained from the PRS. Information on maternal glycosylated hemoglobin (HbA1c) was collected from the patients' records.

The PI-DV was calculated automatically by the ultrasound systems according to Gosling et al, (1971) in 128 cases. The remaining 14 were calculated manually. In order to investigate the impact of IUGR on the results, a sub analysis of PI-DV was performed in which SGA infants and infants with abnormal umbilical blood flow class (I-IIIB) were excluded.

Statistical analysis

All statistical analyses were performed using Gauss software (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com).

The longitudinal reference ranges for DV flow velocities published by Kessler et al. (2006) were used as reference data. The PI-DV values in our study were transformed by the method explained in the appendix in the article by Kessler et al. (2006), and expressed as standard deviation scores (SD-scores) from the transformed reference PI-DV values according to the gestational age. For the DM and GDM groups, 95 % CI for the SD-scores were computed under the assumption of normal distributions.

Non-parametric Wilcoxon test was used for continuous data and Fisher's exact test was used for binary outcome parameters. The correlation between HbA1c levels and PI-DV was calculated, expressed as Pearson rho.

Paper 2

All individuals born in Sweden 1973-1988 (n=1 551 603) were included in the study. Data was merged from the MBR, SPDR and IPR. Three comparisons were made. First, the risk for future non mal-formational cardiovascular disease (NMCVD), defined as consumption of CVD medication (see below), among offspring exposed to maternal DM was compared to the corresponding risk among offspring not exposed to maternal DM. Secondly, the association between SGA and LGA, respectively, and future risk for NMCVD was investigated among offspring without intrauterine exposure to maternal DM.

Cardiovascular disease was defined as consumption, of one or more of the following drugs; platelet aggregation inhibitors (Clopidogrel, B01AC04; acetylsalicylic acid prescribed only as an aggregation inhibitor, (B01AC06), organic nitrates (C01DA), digitalis glycosides (CO1AA), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), and agents acting on the renin-angiotensin system (C09) between 2005-2010.

To examine the risk of medication for NMCVD, offspring with congenital cardiac or renal malformations, cardiac valve disorders, pericarditis, endocarditis, myocarditis, glomerular renal disease, renal failure (main exclusion criteria) were excluded from the final analyses.

Statistical analysis

ORs were calculated according to the Mantel-Haenszel (1959) procedure. 95% CI were calculated according to Miettinen (1974). Stratification was made for the offspring's year of birth, maternal age, and parity. When specified, stratification for offspring with insulin dependent DM was performed.

Paper 3

A linkage was performed between the MBR, SGR and ER including 877 618 full-term singletons born 1973-1986 to Swedish born women. Children who are diagnosed with a mental retardation do not enter the Swedish compulsory school. They are educated in special schools and their possible grades are not reported to the SGR. After excluding children who died or emigrated before 16 years of age, the assumption was made that children without graduation grades who weren't enrolled in compulsory school went to a special school due to cognitive impairment. Also, neonates that were stillborn, had congenital malformations or were SGA were excluded.

During 1988 – 1997, henceforth period one, the school grades were numerical on a five-level scale, with one as the lowest and five as the highest grade. From 1998 and onwards, henceforth period two, the grades are alphabetical with four levels: not passed (NP), passed (P), passed with distinction (PD), and passed with excellence (PE).

During period one, it was possible for the students to choose between a common or an advanced course in mathematics. During period two, all students took the same mathematics course. A possible confounder influencing the results could be that adolescents who had low Apgar scores at birth would be more likely to choose the common course in mathematics rather than the advanced course. Therefore, results on low Apgar scores and school grades in mathematics are only from period two. During period one we present only the odds of choosing common or advanced mathematics.

First, the association between Apgar score <7 at 5 minutes after birth and need of education in special school, or leaving school without any graduation grades at all, was evaluated. Secondly, the level of the grades among children graduating from compulsory was investigated. For that investigation, the grades were divided into class variables (for period one: lacking, 1, 2, 3, 4, or 5; for period two: lacking, NP, P, PD, PE). The mentioned class variables were compared to most common level (3, or P respectively).

The association between Apgar scores <7 at 5 minutes after birth and school achievement was evaluated using the Mantel-Haenszel (1959) procedure to produce stratified ORs. Approximate 95% CI were calculated using the method proposed by Miettinen (1974). Stratification was made for the year

of birth, maternal age at delivery, parity, maternal smoking, and maternal final educational level.

Statistical analysis

The impact of maternal risk factors on the offspring's need for special school was evaluated by the Manzel-Haenszel test, and adjusted for year of child's birth, maternal age, parity, smoking, and educational level.

When comparing two adjusted ORs, two-tailed z tests were carried out, under the assumption of normal distribution of the log ORs. In order to detect a putative linear trend in stratified OR:s along I one-step-Apgar-strata, weighted linear regression analyses of the log (OR_i:s) were carried out, where each log(OR_i) was weighted according to precision ($weight_i$=1/Variance of log(OR_i)).

Paper 4

During the period 1990-2007, 13 491 births to women with either DM (n = 3 226) or GDM (n= 10 265) from complete 38 weeks of gestation or beyond were found in the MBR. A linkage was performed with IPR to assess long term neurological disease depending on mode of delivery.

The risk of Apgar score <7 at five minutes after birth was compared in new-borns to women delivered by planned CS at 38 completed weeks with those born at 39 completed weeks or more (irrespective of mode of delivery). The analysis was performed in 4 sets, women with GDM, DM, a composite group of DM+GDM, and the LGA-group.

Statistical analyses

All statistical analyses were performed using Gauss (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com).

ORs with 95 % CI for Apgar <7 at five minutes after birth were calculated using multiple logistic regression. The following variables were evaluated as possible confounders: fetal year of birth, fetal weight SD-scores, fetal malformations, GDM (in the DM + GDM group), maternal age, parity,

smoking, and BMI. Hazard Ratios (with 95% CI) for CP or EP were computed using Cox analyses considering the different lengths of follow up within the study group.

Paper 5

In this study, the NDR and the MBR were merged, including 1 873 440 women, born 1930-1989. Cases with either type 1 DM (n=3467) or type 2 DM (n=35 041) were identified from the NDR. Fetal birth weight was extracted from the MBR.

The analyses regarding risk for future DM in relation to birth weight in the offspring were based on the last delivery before the occurrence of a diagnosis of DM. All women diagnosed with DM before the birth of their first child or DM/GDM during pregnancy were excluded from the analysis. In a subgroup of women giving birth after 1986, the risk of future type 1 or type 2 DM was analyzed in women with a diagnosis of GDM.

Statistical Analysis

ORs for future DM were estimated using the Mantel Haenszel technology, and 95% CI were estimated using the method proposed by Mietinnen (1974). The ORs were stratified for maternal year of birth, year of delivery, parity, country of origin, presence of preeclampsia/eclampsia. In a smaller subset of data, stratification was performed for BMI and maternal smoking.

In order to detect a putative linear trend in stratified OR:s along i time classes to disease (eg DM), weighted linear regression analyses of the log (OR_i:s) were performed, where each log(OR_i) was weighted according to precision (weight$_i$=1/Variance of log(OR_i)).

The incidences of Type 1 and Type 2 DM, respectively, by presence of LGA and year of birth since the last delivery, were illustrated using Kaplan Meier estimates.

RESULTS AND COMMENTS, PAPER 1-5

Paper 1

Results

In this study we showed that DV-PI SD-scores in diabetic pregnancies, complicated by either GDM (P = 0.006) or DM (P = 0.0015) are increased compared to previously published normal references ranges (Kessler et al, 2006) (Figure 3). In the DM group, the mean PI-DV was 0.56 (95% CI 0.52-0.59) and the mean PI-DV SD-score was 0.37 (range 0.14-0.59). The corresponding means in the GDM group were 0.55 (95% CI 0.51-0.60) and 0.38 (range 0.11-0.65). We also showed a positive correlation between maternal glycemic control, measured by HbA1c, and increasing DV-PI S.D-scores in DM pregnancies (Pearson rho = 0.31 (95% CI, 0.04–0.54) The mean HbA1c values in the group with PI-DV SD scores ≤0 was 4.7 (95% CI 4.5-4.9 and 5.4 (5.0-5.7) (p= 0.003) in the group with PI-DV SD scores >0, the last month before the last DV-measurement (Figure 4).

When SGA fetuses or with abnormal umbilical artery BFC (UA BFC) were excluded, the mean DV-PI SD-scores were still statistically significantly increased in both the DM (p = 0.02) and GD group (p = 0.035).

Figure 3. Pulsatility index of ductus venosus (PI-DV) in relation to gestational age at examination and according to type of diabetes. Reference values obtained from Kessler et al.

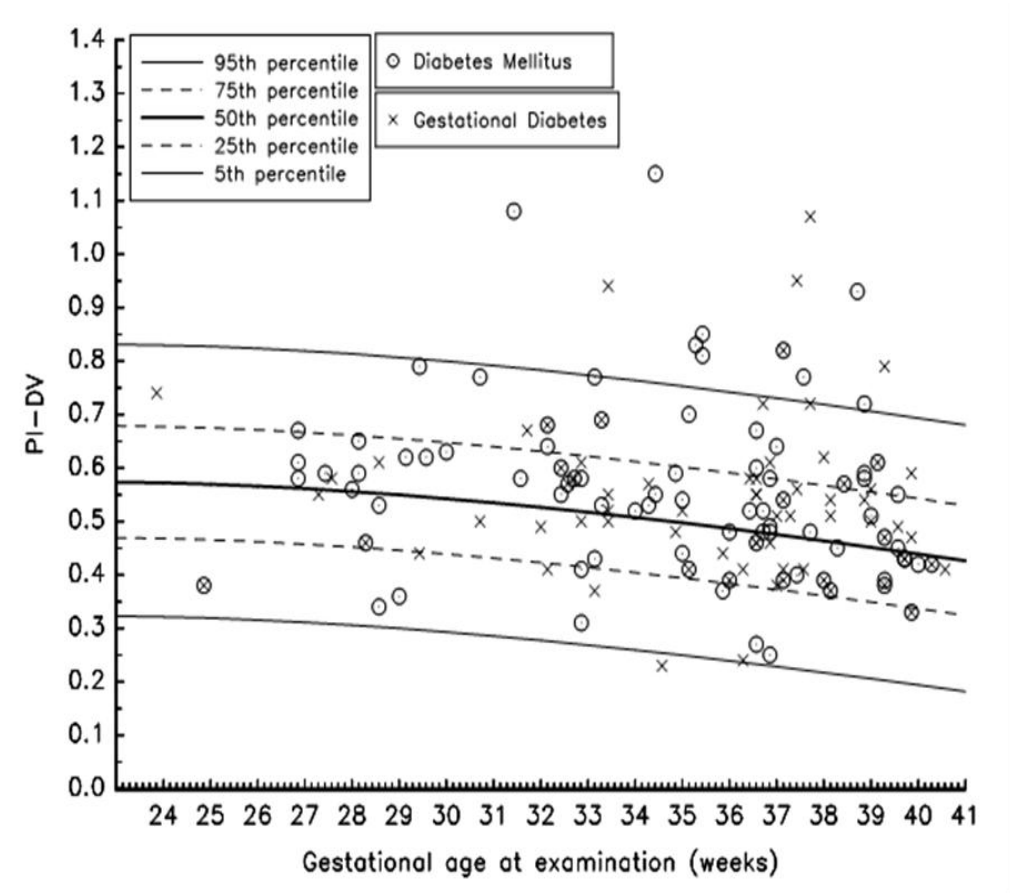
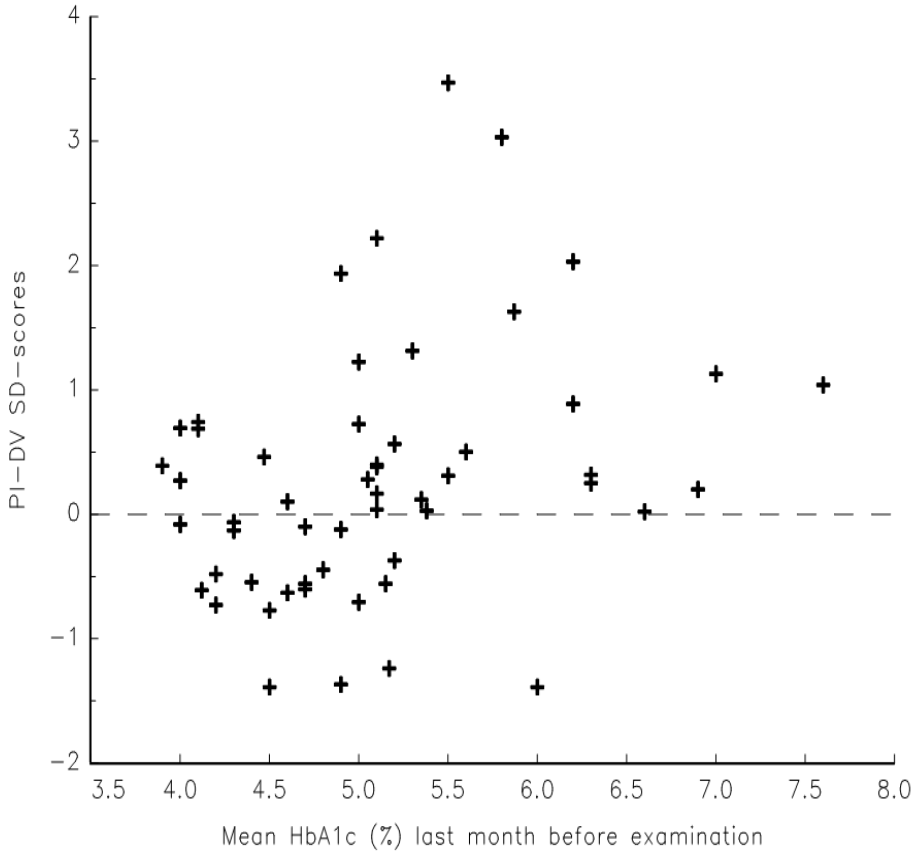


Figure 4. Mean HbA1c in DM- pregnancies the last month before the last DV measurement before delivery plotted against PI-DV SD-scores.



Comments

The study confirms previous reports in which both fetuses to diabetic pregnancies and fetuses with cardiac disease exhibit altered blood flow in the DV (Montenegro et al, 1997) (Zielinsky et al, 2004)(Girsen et al, 2007 and 2008)(Mäakikallio et al, 2002)(Yli et al, 2008).

Interestingly, we found a positive correlation between maternal HbA1c and increased DV-PI SD- scores in DM women with eminent glycemic control (mean HbA1c= 5.2). However, Jaeggi et al, (2001) previously showed increased thickening of the myocardium in fetuses to diabetic women with near normal HbA1c (mean HbA1c= 5.9) in mid and late trimesters. In our study, a correlation between maternal HbA1c and DV-PI SD scores could only be found in the later part of pregnancy. This finding was confirmed in a recent study, in which no difference in DV-PI was found between poorly controlled diabetics (mean HbA1c =7.5) and a normal control group in the first trimester (Turan et al, 2011). Poor glycemic control in early gestation might mostly influence the incidence of cardiac congenital malformations, rather than blood flow changes in DV. Maternal hyperglycemia might lead to structural changes in the myocardium which can be assessed by blood flow measurements in the DV only in the later parts of gestation.

Our study population consisted of a high risk population with a high prevalence of comorbidities, such as preeclampsia, know to effect placental hemodynamics. Therefore, we performed a sub- analysis in which fetuses with abnormal UA BFC or who were SGA were excluded. However, the increased DV-PI S.D scores were still significantly increased in both DM and GDM pregnancies.

A drawback to our study was the lack of normal longitudinal reference ranges of DV-PI, therefore we used reference ranges by Kessler et al (2006), composed of 160 low-risk Norwegian pregnancies, with over 500 measurements. The Norwegian population of normal low risk pregnancies exhibits the same anthropologic traits as a corresponding Swedish population. As DV-PI is dependent of gestational age, we chose to transform the absolute DV-PI values to S.Ds of the expected DV-PI for gestational age.

In an attempt to investigate the capability of DV as a predictor of adverse neonatal outcome, Wong et al (2010) studied 83 diabetic pregnancies, of which 30.5% had an abnormal peak velocity index of the DV (+ 2 S.D). The ability of an abnormal DV-index to predict adverse perinatal outcome (CS, SGA, cord-blood arterial pH <7.2, 1-min Apgar score ≤3.5-min Apgar score

<7, hypoxic ischemic encephalopathy, stillbirth or neonatal death) was 32%, and therefore not of satisfactory sensitivity to use for screening purposes in diabetic pregnancies. Analogously, in our study, among fetuses to DM, two were stillborn, and one died within 24 h after birth, giving a total perinatal mortality rate of 3.5%. All three fetuses had DV-PI within normal limits; the DV recordings were performed 6 weeks, 1 week and 2 days prior to delivery, respectively. No deaths occurred in the GDM group.

Study 2

Results

The study comprised 1 551 603 individuals of whom 3 534 were born to mothers with DM during pregnancy. Among offspring to mothers with DM, 96 (2.7%) were excluded due to main exclusion criteria, and 80 (2.3%) had insulin dependent DM. Among mothers without DM, 21 643 (1.4%) were excluded due to the main exclusion criteria, and 7965 (0.5%) had insulin dependent DM.

The results are shown in three sub analysis in Table 3, both crude OR + 95% CI and after adjusting for year of delivery, maternal age and parity.

1. Before excluding our main exclusion criteria: offspring with congenital cardiac heart disease, renal congenital malformations and renal failure.
2. After excluding main exclusion criteria.
3. After excluding main exclusion criteria and also adjusting for offspring with insulin dependent DM.

An increased risk for NMCVD was found in sub analysis 1 and 2 (Table 3), but the increased risk was no longer statistically significant after adjusting for offspring with insulin dependent DM (adjusted OR: 1.22, p=0.09).

Offspring to mothers with DM, had an increased risk of insulin-dependent DM, adjusted OR= 4.7 (95% CI 3.9-5.8). Among offspring to mothers with DM, offspring with insulin dependent DM had an increased risk of NMCVD, adjusted OR=24.6 (95% CI 13.6-44.4) compared to offspring without DM.

In non-diabetic pregnancies, we found an increased risk of CVD in offspring born SGA, but not LGA when compared to AGA offspring (Table 4).

Table 3. Risk of cardiovascular disease in offspring in relation to exposure to maternal diabetes mellitus (DM). IDDM: insulin dependent diabetes mellitus. [A] Exclusion of offspring with congenital heart disease, kidney malformations and kidney failure/glomerulonephritis [*]Adjustments were made for year of delivery, maternal age and parity, using the Mantel-Haenzsel technique.

	Maternal DM			No maternal DM (reference)
	n(%) with heart medication	Crude OR	Adjusted OR (95% CI)	n(%) with heart medication
No exclusions	86 (2.4)	1.1	1.5 (1.2-1.8)	35 389 (2.3)
After exclusion of offspring with main exclusion criteria [A]	77 (2.2)	1.0	1.5 (1.2-1.8)	32 886 (2.2)
After exclusion of offspring [A] and adjusting for offspring IDDM	77 (2.2)	1.0	1.2 (0.9-1.5)	32 886 (2.2)

Table 4. Risk of cardiovascular disease in offspring in relation to weight according to gestational age. [A]Exclusion of offspring with congenital heart disease, kidney malformations and kidney failure/glomerulonephritis. IDDM: insulin dependent diabetes mellitus. NS: not significant.

	SGA N= 81 531			AGA N= 1 409 357		LGA 57 181		
	n(%) with heart medication	Crude	Adjusted	n(%) with heart medication		n(%) with heart medication	Crude	Adjusted
		OR	OR (95% CI)	Reference				OR (95% CI)
No exclusions	2 592 (3.2)	1.4	1.3 (1.3-1.4)	31 510 (2.2)	1.0	1 287 (2.3)	1.0	1.0 (1.0-1.1) NS*
After exclusion of offspring with main exclusion criteria [A]	2 340 (2.9)	1.4	1.3 (1.2-1.3)	29 364 (2.1)		1 182 (2.1)	1.0	1.03 (0.97-1.1)
After exclusion of offspring [A] and adjusting for IDDM	2 340 (2.9)	1.4	1.3(1.2-1.4)	29 364 (2.1)		1 182 (2.1)	0.99	1.02 (0.96-1.08)

Comments

In study 2, influenced by the "fetal programming" hypothesis, we investigated if exposure in utero to maternal diabetes could have an impact on the fetus risk of cardiovascular disease as a young adult. We also wanted to investigate if offspring with impaired or excess intrauterine growth, in non-diabetic pregnancies, was associated with future cardiovascular disease.

Since the risk of insulin dependent DM in the offspring to insulin dependent diabetic mothers is increased (Warram et al, 1984), and a risk factor for cardiovascular disease, we stratified for offspring insulin dependent DM, as measured by the prescription of insulin in the SPDR, in sub analysis 3. After adjusting for insulin dependent DM in the offspring, no increased risk of NMCVD could be found. We therefore interpret the increased risk of NMCVD to be mainly due to offspring DM rather than to fetal exposure to hyperglycemia.

One cannot rule out, however, that both exposure to maternal DM and subsequent development of own DM, can have an additive risk effect. The "two-hit" hypothesis was originally coined by Alfred Knudson (1971) to explain the origin of childhood retinoblastoma, e.g. where both tumor suppressor genes need to be mutated to develop the disease, and further has also been used as an explanation for liver steatosis (Day and James, 1998). The first hit leads to fatty liver, the second hit to lipid peroxidation and steatosis. In analogy with the "two-hit" theory one can speculate if, in the occurrence of cardiovascular disease; the first hit is exposure to maternal DM during intrauterine life and the second hit is an individual's own DM or other risk factors.

However, even if we could confirm the already established association between being born SGA and future cardiovascular disease, some methodological difficulties should be addressed. Firstly, the offspring studied are at the oldest 37 years of age, an age when cardiovascular disease has not yet reached its peak, and therefore the study probably underestimates the frequency of disease. Secondly, it is most likely that those using CVD medication use it for hypertension. The negative result therefore cannot be interpreted as the absence of a relation of fetal exposure to maternal DM with CVD in adults.

Also, some of these medications can be used for other indications, migraine, Raynaud phenomenon, tremor, anxiety, stage fright, and might

not measure CVD, however individuals taking medicine for other indications should be randomly distributed among both offspring to diabetic and non-diabetics and therefore should not influence the ORs.

Paper 3

Results

Among infants born with an Apgar score <7 at 5 minutes after birth, an increased risk of needing education in a special school was found, OR=1.93 (95% CI 1.75-2.14). The corresponding risk estimate when born with an Apgar score 0-3 at 5 minutes after birth was 2.13 (95% CI 1.81-2.52). One of 44 children born with an Apgar-score <7 at 5 minutes after birth will need education in a special school due to the factors leading to the low Apgar score. Also, for every one step decrease in the Apgar score, a linearly increased risk of needing education in a special school was found ($p<10^{-6}$).

Among the children in need of education in a special school, 910 (4 %) received the diagnosis neonatal asphyxia. Among children graduating with grades, 24 123 (2.8%) received the diagnosis neonatal asphyxia. The association between neonatal asphyxia and need of education in a special school was statistically significant, OR =1.43(95% CI 1.33-1.52). The association between the need of education in a special school and an Apgar score<7 at five minutes after birth was stronger than the association between the need of education in a special school after receiving the diagnosis neonatal asphyxia ($p<10^{-6}$).

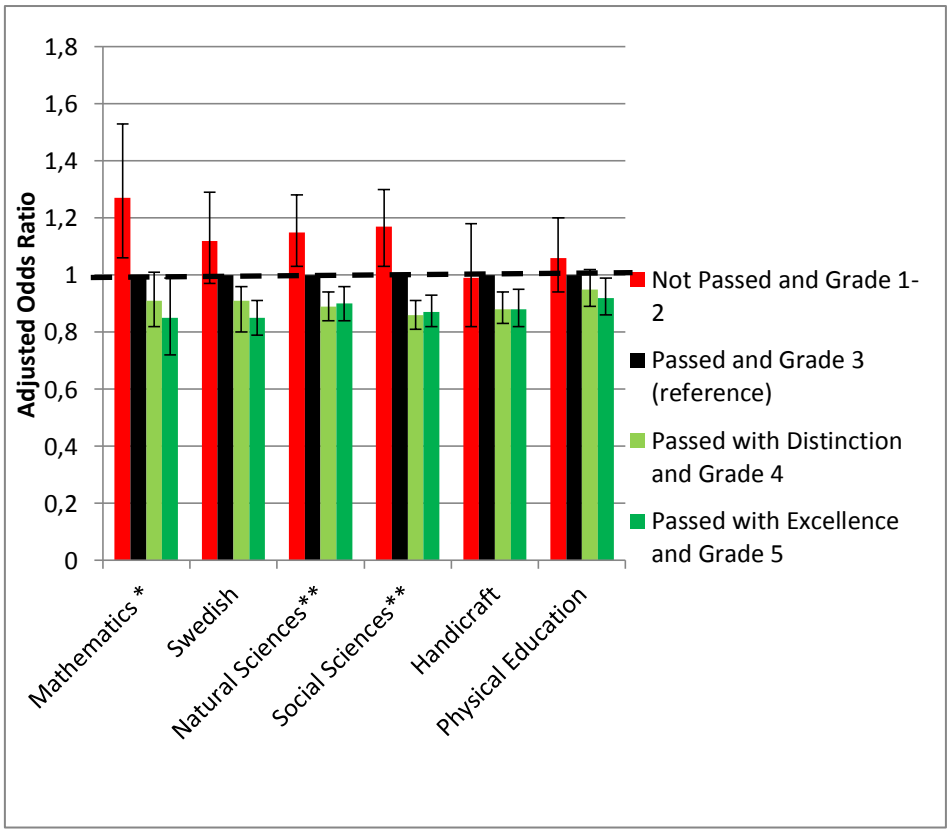
The risk of graduating from compulsory school without any grades in any subjects (n=61), when born with an Apgar-score <7 at 5 minutes after birth, was not significant OR =1.23 (95% CI 0.95-1.58).

In Figure 7, the distribution of school grades in six different school subjects (mathematics, Swedish, natural sciences, social sciences, handicraft and physical education) when graduating from compulsory school are shown. The risk of graduating from compulsory school without any grades in a specific subject was increased for nearly all individual schools subjects, when born with an Apgar score <7 at five minutes after birth. Also, as seen in Figure 7, when born with an Apgar score <7 at five minutes after birth, an increased risk of receiving lower grades (NP or grade 1-2), and lower

probability of receiving the higher school grades (PD, PE or grade 4-5) was found in nearly all subjects.

As specified in the material and methods section, the distribution of grades in mathematics was only analyzed in period two, during which only one combined course in mathematics was offered. During period one, the adolescents could choose between a common or advanced course in mathematics. During period one, the adolescents with Apgar score < 7 at five minutes after birth showed a higher risk of graduating without a grade in advanced math OR=1.14 (95%CI 1.08-1.21), assumingly because they were more prone to choose common mathematics.

Figure 7. The effect on school grades in different subjects when graduating from compulsory school 1988-2003 after having an Apgar score <7 at 5 minutes after birth. Odds ratio and 95% confidence intervals are shown. *Grades from period two, ** Combined estimate.



Comments

The goal of study 3 was to elucidate the capability of a low Apgar score (<7 at five minutes after birth) to predict long term mild neurological dysfunction, and consequently its ability to be used as a marker in evaluating obstetrical care. In this large study, comprising almost 900 000 individuals, we showed an increased risk of needing education in a special school and receiving no or lower grades, and a lower probability of higher grades when graduating from compulsory school at 16 years of age, after being born with a low Apgar score.

In order for the low Apgar score to reflect potential hypoxic events during labor, and not antenatal factors, we included only term, non SGA, newborns to Swedish mothers and fathers without malformations or chromosomal aberrations, not expected to exhibit low Apgar scores at birth.

Asphyxia is one of the main causes of neurological damage in infants (Thornberg et al, 1995), leading to future disabilities. Three issues regarding asphyxia should be briefly commented; the definition, timing, and predictive value of markers of asphyxia.

No single clinical, laboratory or diagnostic tool can be used alone in defining asphyxia. As single markers, the Apgar score and umbilical cord pH are commonly used. Most children with low 5 minute Apgar scores develop no neurological sequel, and 75 % of children who developed CP have normal 5 minute Apgar scores (Nelson et al, 1981). Also, the Apgar score received will be influenced by the midwife or pediatricians subjective perception of the clinical status of the newborn. Furthermore, no clear cut threshold exists between low cord blood pH and neurological sequel (Yeh et al, 2012). An association exists between low cord blood pH and CP, but once again the vast majority of infants born with cord blood pH under 7 turn out healthy and most are born with a higher cord blood pH value than this.

The American Academy of Pediatrics and the ACOG (2003) have together defined perinatal asphyxia including ALL of the following: (1) profound metabolic acidosis (pH < 7.00); (2) persistence of an Apgar score of 0 to 3 beyond 5 minutes; (3) clinical neurologic sequel in the immediate neonatal period that include seizures, hypotonia, coma, or neonatal encephalopathy (HIE); and (4) evidence of multi organ system dysfunction in the immediate neonatal period.

Regarding the timing of an acute intrapartum hypoxic event as the cause of subsequent cerebral palsy similar criteria have to be fulfilled (ACOG 2003) (1) evidence of metabolic acidosis (pH < 7) and (2) early onset of severe or moderate neonatal encephalopathy. Other useful criteria that were thought to be supportive but not essential included (a) a sentinel event (e.g., cord prolapse, uterine rupture, placental abruption); (b) a sudden, rapid, and sustained deterioration of the fetal heart rate; (c) an Apgar score below 6 after 5 minutes; (d) early evidence of multisystem involvement; and (e) early evidence of acute cerebral abnormality.

The above definitions are quite extensive, and most studies have focused on single markers (Apgar score, cord pH) in the prediction of long term outcome (Thorngren-Jerneck 2001)(Moster et al, 2001)(Lie et al, 2010)(Beeby et al, 1994). The predictive value of a low Apgar score has been questioned, but yet, the Apgar score is one of the few easily assessable, low cost, and globally used markers available. A large Swedish study found 31 times increased risk of CP, 8 times increased risk of EP, almost 10 times higher risk of mental retardation and 14 times higher risk of infant mortality rate after being born with an Apgar score <7 at five minutes after birth. In a meta-analysis analyzing different assessment scores in newborns predicting neonatal deaths, a common OR of 20 in predicting neonatal death when having a 5 minute Apgar score of 4-6, compared to 7-10 (van de Riet et al, 1999) was found. Most studies have focused on short term follow up of severe morbidity. Both Odd et al (2008) and Ehrenstien et al (2009), however, showed an increased risk for poorer scoring on IQ tests in men drafting for the military, when born with an Apgar score <7 at five minutes after birth.

Our results from paper 3, are used to substantiate the use of Apgar score <7 at 5 minutes after birth, as marker of neonatal outcome in paper 4.

Paper 4

Results

Among all diabetic women in 38 full gestation weeks, an elective CS was performed in 1 305 (28.2 %) of cases. At 39 completed weeks of pregnancy or more, a total of 12 186 births took place, 8 842 (73%) vaginal, 1042 (8.6%) vaginal instrumental, 1630 (13.3%) emergency CS, and 671 (5.5%) elective CS. In the planned CS group, 35% of the infants were LGA, and 12.5% in the planned vaginal group.

Sixty-seven infants (2.1%) in the DM group had Apgar score <7 at five minutes after birth and 134 (1.3%) infants had Apgar score <7 at five minutes after birth in the GD-group.

In the DM+GDM group a significantly reduced risk of Apgar scores <7 at five minutes after birth was found in the planned CS group versus the planned vaginal group (p= 0.021) (Table 5). No significantly reduced risk of Apgar score <7 at five minutes after birth in the planned CS group versus the planned vaginal group was found in the DM group OR = 0.45 (95% CI 0.19-1.11) (p=0.08) or GD group alone OR =0.55 (95%CI 0.26-1.17) (p= 0.12).

In both diabetic groups, a total of 1 981 (14.7%) infants were LGA, of whom 8 infants (1.8%) had Apgar score <7 at five minutes after birth in the planned CS group versus 36 (3.54%) in the planned vaginal group. With a multivariate logistic regression model that included age, age (second grade model), birth weight SD-score (second grade model), parity and planned CS, the adjusted odds ratio for Apgar scores <7 at five minutes after birth was 0.47 (95% CI 0.21-1.03) (p=0.06) in the LGA group, planned CS versus planned vaginal delivery.

The study was not dimensioned to analyze other outcome measures such as perinatal death (n= 57) or neonatal morbidity, and no significantly reduced risk of perinatal death (OR =0.6 (95% CI 0.23-1.62) (p= 0.3) was found. In the univariate model the hazard ratio for either CP (n= 5) or EP (n=70) was 1.58 (95% CI 0.58-4.35)(p=0.37), between the planned vaginal and planned CS group.

Table 5. Association between Apgar score <7 at five minutes after birth and planned mode of delivery in both diabetic groups. [A]The multivariate model includes all variables shown in the column. All variables with p<0.2 in the univariate analyses were entered in the multiple model. Abbreviations: CS cesarean section; GDM; gestational diabetes mellitus; DM diabetes mellitus type 1; BMI body mass index; SD standard deviation weight scores; OR odds ratio; CI confidence interval.

	DM and GDM			
	Univariate		Multiple model[A]	
Investigated variables	OR	95%CI	OR	95%CI
Elective CS completed 38 weeks	**0.75**	**0.44-1.27**	**0.51**	**0.28-0.90**
GDM (vs DM)	0.62	0.46-0.84	0.67	0.49-0.92
Maternal age, second grade model[A]				
Linear term	0.73	0.59-0.90	0.82	0.66-1.01
Quadratic term	1.01	1.00-1.01	1.00	1.00-1.01
Nulliparity	2.42	1.82-3.20	2.72	2.00-3.71
Maternal smoking (yes vs no)	0.98	0.65-1.49		
Maternal BMI (one step increment)	1.04	1.02-1.07	1.05	1.02-1.08
Significant malformation	2.03	1.10-3.77	1.80	0.96-3.36
SD-scores (one step increment, quadratic term)	1.07	1.05-1.10	1.09	1.06-1.12
Year of delivery (one year increment)	1.01	0.98-1.04		

Comments

Given the high frequency of adverse neonatal outcome and instrumental deliveries in diabetic pregnancies, we wanted to investigate if a planned CS could have a protective effect, as measured by risk of 5-minute Apgar score <7. As our results revealed that a CS needs to be performed 132 times (NNT) to avoid one low 5-minute Apgar score, one can, however, question the "clinical sense" to offer all diabetic women an elective CS.

In the multivariate analysis, the DM + GDM group showed a significantly decreased risk of low Apgar scores in the planned CS group versus planned vaginal group. The corresponding risk estimates in the DM, GDM and LGA groups alone were of the same magnitude, but did not reach statistical significance, perhaps due to small sample size.

A small collection of studies exist in regards to when and how to deliver the diabetic fetus (Boulvain et al, 2001) (Kjos et al, 1993)(Conway et al, 1998). Ethical difficulties exist when designing a randomized controlled trial assessing outcome after planned CS versus planned vaginal delivery in diabetic pregnancies. We therefore chose to use information in the MBR. Planned mode of delivery is not entered as a variable in the MBR, only actual start of labor. Therefor an attempt was made to construct a study model to assess the actual planned mode of delivery. An assumption was made that only the presumed healthiest mothers and fetuses were allowed to continue pregnancy and aim for a vaginal delivery, leading to a higher proportion of inherent risk factors, both maternal and fetal, in the planned CS group. The mothers in the planned CS group were older, had a higher BMI and a larger percent of the babies were LGA and had malformations.

The vast majority of planned CS were performed in gestational week 38 (n= 1305). In order to avoid miss classification of an emergency CS as an elective CS, as in the example of when women planned for an elective CS entered the delivery ward with labor pains, the planned vaginal group was defined as those starting labor after 39 full weeks of gestation.

In gestational weeks 39+0 – 43+0, 671 planned CS were performed. Three alternatives are given how to deal with these: exclude them, allocate them to the planned CS group, or allocate them to the planned vaginal group. We decided to allocate them to the "planned vaginal group".

We assumed that the vast majority were true classifications of planned CS in, primarily gestational week 39 and 40. As mentioned above, only the presumed healthiest pregnancies were allowed to continue pregnancy past

gestational week 38, if complications had occurred before, the patient would have been delivered. If an assumed "healthy" pregnancy was allocated to "the planned CS group", our results would show false high protective value of a planned CS.

On the other hand, some planned CS beyond gestational week 38 could be misclassifications of emergency CS. A hypothetical example might be: the woman was planned for a vaginal delivery, was admitted to the labor unit due rupture of the membranes without contractions in gestational week 40, an un ripe cervical status was found, and fetometry gave suspicion of a 5 kilogram fetus, the mother fasted over night and was delivered by (semi) elective CS the next morning.

We believe these cases to be few, but if misclassified emergency CS were allocated to the planned CS group, a false high morbidity would spill over to the planned CS group, leading to false low risk estimates when comparing planned CS versus planned vaginal delivery.

If women receiving the ICD code for planned CS past gestational week 38 group were excluded, uncertainty would reign regarding exactly who was excluded. We therefore decided to keep them in the planned vaginal group, and this way the risk estimate would be "conservative", and no false increased risk estimate benefiting the planned CS group would be showed. This systematic bias makes it probable that the true protective effect of an elective CS to prevent low Apgar scores might have been even stronger than the estimates obtained in our study.

Paper 5

Results

Our study included 1 873 440 women born between 1930 and 1989, of whom 3 467 women were diagnosed with type 1 DM and 35 041 women with type 2 DM, after delivery.

Eighty percent of the women who developed type 2 DM had a BMI of > 25 at their first visit to the antenatal clinic. No association was found between maternal BMI and future type 1 DM. Women with BMI <20, compared to BMI 20 to 24, exhibited a 50% lower risk of future type 2 DM, adjusted OR

0.49 (0.38 - 0.64). The corresponding adjusted risk estimate for women with BMI >35 was OR 28.41 (25.89 - 31.17).

An increased risk of developing either type 1 OR=3.46 (95% CI 3.12-3.83) or type 2 DM, OR= 2.90 (95% CI 2.80-3.01) was found subsequent to giving birth to a LGA child. Women giving birth to a SGA child, also had an increased risk of developing type 2 DM, OR 1.13 (95% CI 1.08-1.19) but not type 1 DM OR=1.10 (95% CI 0.93-1.30).

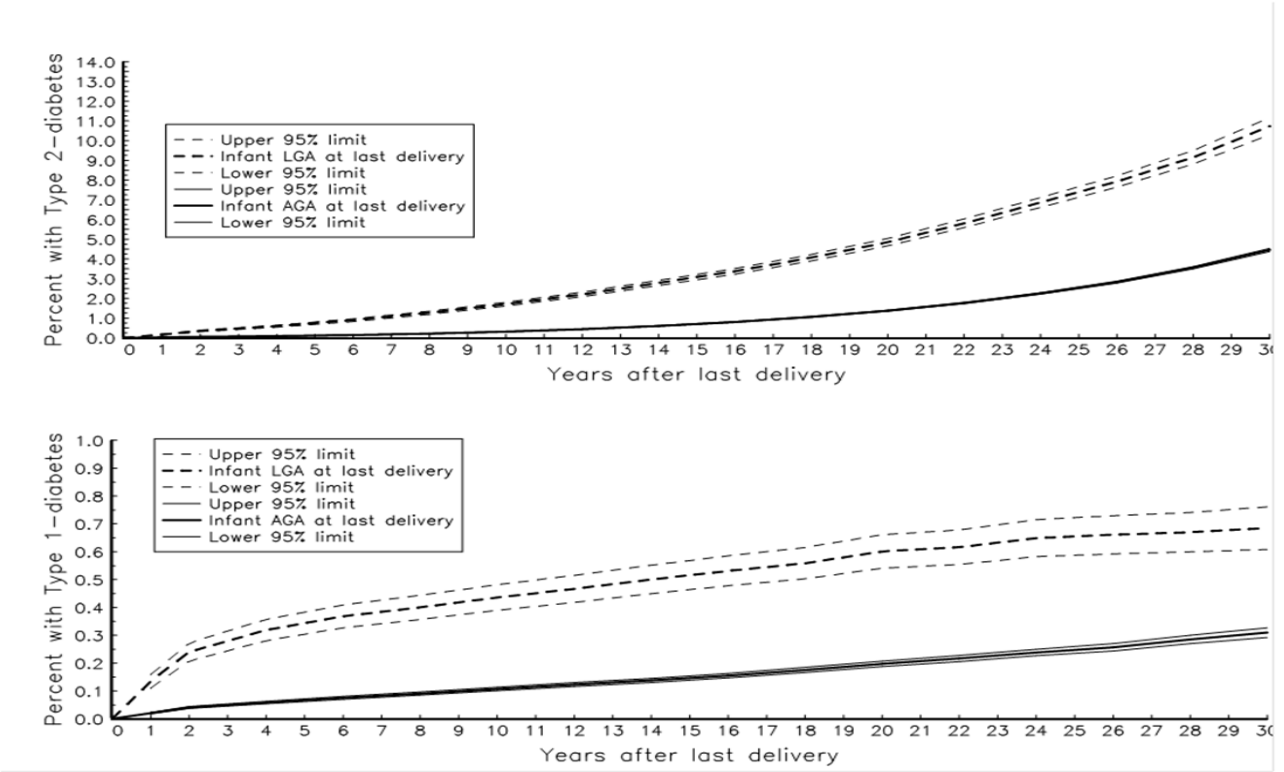
After adjusting for smoking and maternal BMI, and therefore restricting the analysis to births 1983 or later, the risk of a type 2 DM diagnosis after giving birth to a SGA child was still increased, OR 1.11 (95% CI 1.03-1.21). The risks of subsequent type 1 or type 2 DM, after giving birth to a LGA child remained increased, OR 3.76 (95% CI 3.31-4.27) and OR 3.37 (95% CI 3.21-3.54), respectively, and the risk estimates were in the same magnitude as when not adjusting for BMI and smoking.

After giving birth to a LGA child, the risk of developing type 1 or type 2 DM within one year from delivery, was 9 and 11 times higher, respectively when compared to the risk of developing DM after giving birth to offspring with a birth weight within +/- 1 S.D. Still 10 years later, the increased risk was still present, 1.72 (95% CI 1.41 - 2.11) for type 1 DM and 2.46 (95% CI 2.36 - 2.56) for type 2 DM. The magnitude of the association between LGA and future type 1 and type 2 DM decreased linearly with time (p for trend$<10^{-6}$).

When giving birth to offspring with a birth weight below 2500 grams, the risk was increased for both type 1 DM, OR 1.35 (95% CI 1.11- 1.66) and type 2 DM, OR 1.50 (95% CI 1.40 -1.61). The corresponding ORs for future DM after giving birth to offspring with a birth weight over 4500 grams was OR=2.84 (95% CI 2.45 - 3.31) for type 1 DM and OR=2.88 (95% CI 2.72 - 3.04) for type 2 DM.

Figure 8 shows the Kaplan Meier estimates for the risk of developing type 1 and type 2 DM after giving birth to LGA offspring over time since last delivery. For type 1 DM, the steepest risk increase was within the first couple of years after last delivery, after that the risk of developing type 1 DM was not higher for women giving birth to LGA infants than for other women. In women developing type 2 DM the risk panorama was different; the risk of developing type 2 DM in women who gave birth to an LGA offspring was present many years after the last delivery.

Figure 8. The recorded prevalence of maternal type 1 and 2 DM over time, in relation to birth weight according to gestational age.



Comments

In study 5 we used fetal birth weight as a mirror of the maternal metabolic status. We found a profound increased risk of developing both type 1 and 2 DM subsequent to giving birth to a LGA or macrosomic infant. Given the current difficulties diagnosing GDM, we believe that a majority of the women giving birth to LGA infants actually had GDM during pregnancy, but never received a diagnosis. GDM is also a risk factor for intrauterine growth restriction (McCance et al, 1994) and we found a slight risk increase of developing type 2 DM, OR= 1.13 (95% CI 1.08-1.19), but not type 1 DM, after giving birth to a SGA infant. However, the risk of developing type 1 DM was slightly increased after giving birth to an infant with a birth weight under 2.5 kg, OR= 1.35 (95% CI 1.11- 1.66). As no increased risk of future type 1 DM was found after giving birth to a SGA infant, the increased risk after giving birth to an infant with a birth weight less than 2.5 kg probably represents premature born infants.

Perhaps surprisingly, we found an increased risk of developing type 1 DM after giving birth to a LGA infant. It has previously been showed that auto antibodies can be detected in serum years before type 1 DM manifests itself clinically (Bingley et al, 1997). Our Kaplan Meier curves revealed that after giving birth to a LGA infant, the steepest increase in the prevalence of type 1 DM is during the first couple years after delivery, after that the prevalence levels off and is not higher than for women giving birth to infants with normal weight. Regarding type 2 DM, the prevalence of disease increases continuously.

In our study, as many as 75% of the women who later developed type 2 DM had a BMI over 25 at the first visit with the prenatal clinic. Pre-pregnancy weight, extensive weight gain during pregnancy and GDM are all risk factors for both giving birth to LGA infants and developing future type 2 DM (Black et al, 2012). As both high pre-pregnancy BMI and GDM commonly coincide, difficulties exist differentiating what proportion high BMI contributes to the increased risk of LGA. A recent study showed that the risk of giving birth to a LGA infant increased linearly in both women with and without GDM. The effects of both high BMI and GDM were additive. The prevalence of LGA infants were similar in obese (BMI over 35) non-diabetic women (12.7%) and normal weight women with GDM (13.6%) (Black et al, 2012).

However, in our study, since the risk estimates of developing future type 2 DM barely differed before and after adjusting for maternal BMI, the

increased risk of future type 2 DM cannot be attributable to maternal obesity.

In 2006 the NDR had an estimated 60% coverage of the diabetic population in Sweden, and during 2008, the estimated coverage was 80%. Hence, the prevalence's reported in our study are underestimated. However, there is no theoretical possibility that only women giving birth to LGA fetuses are included in the registry, and therefore no risk of selection bias exists.

The increased risk of type 2 DM after GDM is well established, the ADA (2009), WHO (1999), and the ACOG (2009) recommend postpartum screening for type 2 DM in this high risk population. Given our results, we propose further studies regarding the benefits of postpartum screening for DM in women giving birth to LGA or macrosomic infants.

CONCLUSIONS, PAPER 1-5

Paper 1

Fetuses to both type 1 and GDM mothers showed increased pulsatility index of the ductus venosus (PI-DV) in relation to gestational age, even after the exclusion of SGA fetuses and those with blood flow changes, presumably reflecting short term cardiac impact.

Paper 2

Offspring exposed to mothers with type 1 DM during pregnancy showed an increased risk of future cardiovascular disease; this increased risk was however no longer present when the results were adjusted for offspring with insulin dependent DM. Offspring born SGA, but not LGA, showed an increased risk of future cardiovascular disease.

Paper 3

The Apgar score is a resourceful marker of obstetrical care, as we found a substantial risk increase of needing education in special schools, low or no grades when graduating from compulsory school, in nearly all school subjects, after being born with a 5 minute Apgar score under 7.

Paper 4

A decreased risk of being born with an Apgar score<7 at 5 minutes was found in DM+GDM pregnancies after planned CS at 38 full gestational weeks, compared to planned vaginal birth at 39 full gestational weeks and

beyond, but no decreased risk of Apgar score<7 at 5 minutes was found in the DM group, GDM group or LGA group alone.

Paper 5

Offspring birth weight is a direct mirror of the maternal metabolic status, as a profound risk increase of developing both type 1 and type 2 DM was found subsequent to giving birth to a LGA or macrosomic fetus.

GENERAL SUMMARY AND CONCLUSIONS

Diabetes mellitus during pregnancy increases the risk of extensive complications for both the mother and fetus.

Fetal exposure to DM is associated with structural changes of the fetal heart, such as cardiac malformations (Wren et al, 2003) and septal hypertrophy (Jaeggi et al, 2001). **In the first paper, an assessment was made of the potential short term cardiac effects after exposure to maternal DM, as measured by aberrations of the pulsatility index of the DV**. Infants to diabetic mothers have previously showed increased cardiac troponin T and pro-B-type natriuretic peptides, both excreted by cardiac myocytes subjected to stress (Goetze, 2009), when compared to offspring to non-diabetic mothers. Levels of pro-B-type natriuretic peptides also correlated with interseptum thickness (Rusell et al, 2009)(Girsen et al, 2009). Rusell et al (2008) have shown that stillborn infants of diabetic mothers have heavier hearts than stillborn infants of non-diabetic mothers after correction for fetal size, suggesting that cardiomyopathy may have a role in "unexplained" fetal death in diabetic pregnancies. Our study confirms the above mentioned impact of maternal diabetes on the fetal heart, as we found increased PI-DV in both DM and GDM pregnancies. Furthermore, a positive correlation between maternal HbA1c levels and PI-DV was found, even though our diabetic mothers had well-controlled DM (mean HbA1c = 5.2).

Not only does fetal exposure to both GDM and type 1 DM, have short term effects, but has also been associated with increased childhood weight in the offspring (Boney et al, 2005). This could be due to fetal programming and in the case of GDM to genes or environmental/eating behavior.

A growing body of literature has confirmed the initial hypothesis from Barker and Hales in the early 1990s (Barker et al 1993)(Hales et al, 1991 and 1992)(Bunt et al, 2005), regarding the influence of the fetal intrauterine milieu on future adult disease. Not only has an increased risk of metabolic diseases been found, but after fetal exposure to maternal DM

also an increased risk of childhood asthma (Azad et al, 2012) and adult neoplasms (Wu et al, 2012).

In the second paper, in an attempt investigate the fetal programming theory; an investigation was performed to assess the risk of long term cardiovascular disease after exposure to maternal DM in utero. Our study could neither confirm nor reject such an association. We found an increased risk of consumption for cardiovascular drugs at the age of 17-36 in adult offspring to mothers with type 1 DM during pregnancy, but the statistical significance disappeared when adjusting for offspring insulin dependent DM. Among offspring to mothers with DM, those with insulin dependent DM had approximately 25 times increased risk of NMCVD, compared to offspring without DM. We therefore interpret the increased risk to be due to offspring DM rather than fetal exposure to maternal DM.

As previously showed by several researchers (Barker et al, 1989) (Andersen et al, 2010) (Rich-Edwards et al, 1997) (Martyn et al, 1996) we could confirm an increased risk of NMCVD in offspring born SGA, but not LGA.

In the third paper, we investigated the association between 5-minute Apgar score <7 and long term academic achievements, in an attempt to substantiate the use of the Apgar score in obstetrical research and hence paper 4. In a large study, including nearly 900 000 individuals, we found a strong association between 5-minute Apgar score <7 and poor academic achievement at 16 years of age. An increased risk of needing education in a special school, receiving low, or no grades was found in almost all subjects. Also, the children born with 5-minute Apgar score <7 had a lower probability of receiving the highest possible grades when graduating from compulsory school. In the absence of better, more easily accessible markers of neonatal outcome, we conclude that the 5 minute Apgar score is a useful marker of obstetrical care.

Newborns to diabetic mothers have an increased risk of low Apgar scores (Persson et al, 2009) and asphyxia (Persson et al, 2009), compared to newborns to non-diabetic mothers. One of the current difficulties within obstetrics regarding the diabetic pregnancy is deciding when and how the women should be delivered. The fetal risks of shoulder dystocia and asphyxia in a vaginal delivery have to be carefully weighed against mainly the maternal risks of an elective CS. **In our fourth paper, we showed an approximately 50% risk decrease of receiving a 5-minute Apgar score <7, in the DM and GDM group, after an elective CS**. Our study was not dimensioned to investigate a potential risk reduction in perinatal mortality. In the group with LGA fetuses, we found a trend

towards a protective effect of a planned CS, but the results were not statistically significant. However, one can question the clinical sense of performing 132 elective CS to avoid 1 newborn with 5-minute Apgar score <7. In summary, the results of study 4, once again stress the high risk nature of the diabetic pregnancy and should be taken into consideration when deciding on mode of delivery, in particular when macrosomia is suspected.

Macrosomia is common among diabetic pregnancies (Persson et al, 2009), and also pregnancies complicated by obesity (Ehrenberg et al, 2004). **Given the current difficulties diagnosing GDM, in the fifth paper, we wanted to investigate if offspring birth weight, in particular high birth weight, could function as a proxy for the maternal metabolic status.** Are we successful in diagnosing all women with DM during pregnancy? We believe that the answer to that question is "no!", as we found a profound increased risk of diagnosis of type 2 DM after giving birth to a LGA fetus. Future studies should include investigations whether it is health economically beneficial to screen women post-partum for DM after giving birth to a LGA infant.

SUMMARY IN SWEDISH

Diabetes under graviditeten innebär ökade risker både för mamman och barnet. Förekomsten av graviditetsdiabetes ökar stadigt, främst pga. ökad vikt hos mamman. Syftet med min avhandling var att undersöka både den kort och långsiktiga risken för hjärtpåverkan hos avkomman till kvinnor med diabetes under graviditeten, undersöka om Apgar-poäng kan användas som mått på förlossningsvården, samt jämföra Apgar-poäng hos nyfödda beroende på om mamman förlösts med planerat kejsarsnitt eller vaginal förlossning, och till sist undersöka mammans framtida risk för diabetes efter det att hon fött ett stort barn.

Avhandlingen innefattade följande fem studier:

Delarbete 1: Blodflödet i duktus venosus hos foster till kvinnor med diabetes

Hjärtmissbildningar är betydligt vanligare hos barn till mödrar med diabetes under graviditeten, och förekommer hos 3-6%. Mätningar av blodflödet i kärlet som leder blodet till fosterhjärtat, duktus venosus (DV), anses återspegla fostrets hjärtfunktion och avvikande flöde med ökat pulsatilt index (PI) har uppmätts hos foster med hjärtmissbildningar, kromosomavvikelser, och hos foster med förhöjd nivå av hjärtsviktsmarkören pro-BNP.

Blodflödesundersökningar av fostercirkulationen erbjuds till alla högriskgraviditeter, inklusive diabetiker. Vi har funnit en ökad risk för förhöjt PI-DV hos foster till gravida diabetiker i jämförelse med en frisk normal population, vilket skulle kunna tala för en påverkan på hjärtat. Vidare har vi visat ett samband mellan moderns långtidsblodsocker, $HbA1_c$, och PI-DV.

Delarbete 2: Diabetes under graviditeten och avkommans framtida risk för hjärtkärlsjukdom

Hypotesen om "fetal origins" hävdar att nutritionella förhållanden i livmodern programmerar fostrets mottaglighet för kroniska sjukdomar som vuxen. Teorin grundar sig på epidemiologiska data som visar ett samband mellan låg födelsevikt och hjärtkärlsjukdom i vuxen ålder. Senare forskning har även visat att hög födelsevikt ökar risken för framtida hjärtkärlsjukdom. Diabetes under graviditeten medför en rubbad ämnesomsättning och en ökad tillgång på näring till fostret, och avkomman är ofta stora.

Genom att samköra information från Medicinska Födelse Registret (MFR) med information från Läkemedelsregistret, har vi jämfört risken för uttag av blodtrycks och hjärtläkemedel som vuxen hos de som exponerats för mammans diabetes under fosterlivet med de som inte exponerats för diabetes under fosterlivet.

Studien innefattade 1 551 603 personer, och visade en ökad risk för uttag av blodtrycks och hjärtläkemedel hos den vuxna avkomman till mammor som hade diabetes under graviditeten. Typ 1 diabetes är dock ärftligt, och typ 1 diabetiker har även en ökad risk för högt blodtryck och hjärtkärlsjukdom. Efter att resultaten justerades för avkomma som själva hade diabetes, kunde inte den ökade risken för hjärtkärlsjukdom hos avkomman påvisas längre. Vi tolkar därför resultaten att det är avkommans egna diabetes snarare än exponeringen för mammans diabetes i fosterlivet som utgör risken för hjärtkärlsjukdom.

Delarbete 3: Relationen mellan låg 5 minuters Agpar-poäng och framtida skolprestation

Apgar-poäng mäts vid 1, 5 och 10 minuters ålder på förlossningskliniker världen över för att kliniskt värdera det nyfödda barnet. Låg Apgar-poäng vid 5 minuter är associerat med ökad risk för cerebral pares, epilepsi och utvecklingsstörningar. Det långsiktiga prognostiska värdet av ett lågt Apgar-poäng är dock ifrågasatt och vi har velat undersöka hur bra Apgar-poäng är som markör för att utvärdera förlossningsvården. Sambandet mellan låg 5 minuters Apgar-poäng och långsiktig kognitiv påverkan har analyserats, genom att titta på associationen mellan Apgar-poäng och

avgångsbetyg från grundskolan (ca 900 000 personer) vid 16 års ålder. Data från MFR har samkörts med Skolbetygsregistret. Genom att även samköra med utbildningsregistret har vi kunnat justera för mammans utbildningsnivå. Våra resultat visar att de barn som hade Apgar-poäng <7 vid 5 minuter har en ökad risk att hamna i särskola, ett av 44 barn som föds med Apgar-poäng <7 vid 5 minuter kommer att kräva skolgång i särskola. Vidare har vi visat att det finns ett rakt samband mellan ett stegs sänkning av Apgar- poäng och skolgång i särskola. Vi har även visat att de barn som hade Apgar-poäng <7 vid 5 minuter barn hade ökad risk att få lägsta möjliga avgångsbetyg samt minskad chans att få högsta möjliga avgångsbetyg från 9:an.

Delarbete 4: Jämförelse av Apgar-poäng hos nyfödda till diabetiker efter planerat kejsarsnitt eller planerad vaginal förlossning

Foster till mammor med diabetes under graviditen löper större risk att utsättas för syrebrist, få andningsstörningar samt blodsockerfall i samband med förlossningen. Nyfödda barn till diabetesmödrar har dessutom ofta hög födelsevikt, och som följd av detta lider de oftare av skador.

De svenska rekommendationerna eftersträvar att gravida diabetiker ska genomgå en vaginal förlossning i fullgången tid. Trots rekommendationerna, är det förvånansvärt många kvinnor som genomgår ett akut kejsarsnitt eller förlossning med sugklocka eller tång. Vi har visat på en ca 50 % lägre risk att födas med Apgar-poäng <7 vid 5 minuter hos diabetiker som genomgår ett planerat kejsarsnitt i jämförelse med de som påbörjar en vaginal förlossning. Det krävs dock 132 planerade kejsarsnitt hos diabetiker för att undvika att ett barn föds med Apgar-poäng <7 vid 5 minuter, och därför är det inte självklart att ett planerat kejsarsnitt bör erbjudas till alla diabetiker.

Delarbete 5: Sambandet mellan fostrets födelsevikt och mammans framtida risk för diabetes

Risken för framtida typ 2-diabetes hos kvinnor som har drabbats av graviditetsdiabetes vid en tidigare graviditet är välkänd och varierar mellan 2-70% beroende på uppföljningstiden. Det råder ingen konsensus hur diagnosen graviditetsdiabetes ska ställas, och man har även observerat ökade komplikationer hos såväl fostret och kvinnan själv, hos de kvinnor som ligger precis under den diagnostiska gränsen för graviditetsdiabetes.

Både kvinnor som är överviktiga och som har diabetes är kända för att föda stora barn, pga. av insulinresistens och ökad näringstillgång till fostret. Samma kvinnor löper framtida risk att få typ 2-diabetes.

Genom att samköra information från MFR och Diabetesregistret har vi undersökt sambandet mellan avkommans födelsevikt och mammans framtida risk att få diabetes, hos kvinnor som inte hade graviditetsdiabetes. Vi har funnit en ca 3.5 gånger ökad risk att få typ 1 diabetes och 2.9 gånger ökad risk att få typ 2 diabetes efter det att kvinnan fött ett stort barn. Efter att kvinnan fött ett stort barn, är risken ca 9 gånger högre att få typ 1 diabetes och 11 gånger högre att få typ 2 diabetes inom ett år efter förlossningen, jämnfört med de kvinnor som föder normalstora barn.

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