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HEALTH OUTCOMES IN OFFSPRING BORN TO MOTHERS WITH TYPE 1 DIABETES MELLITUS

Syventävien opintojen kirjallinen työ
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ÄIDIN TYYPIN 1 DIABETEKSEN VAIKUTUKSET SIKIÖN KASVUUN JA KEHITYKSEEN

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Suomessa tyypin 1 sokeritautia (T1DM) sairastavia ihmisiä on enemmän kuin missään muualla maailmassa ja sokeritautia sairastavien määrä on edelleen jatkuvassa nousussa. Vuosittain noin 350 suomalaista T1DM naista synnyttää, mikä kattaa noin 0.6% kaikista synnytyksistä.

Äidin T1DM lisää huomattavasti erilaisia riskejä sekä äidille että sikiölle raskauden aikana. Useissa tutkimuksissa on havaittu, että T1DM-raskauksissa sikiön kuolleisuus, makrosomia, kasvun hidastuma, synnynnäiset epämuodostumat, sydänlihasrappeuma, raskaudenaikainen hapenpuute ja ennenaikaisuus ovat huomattavasti yleisempiä verrattuna terveiden äitien raskauksiin. Vaikka T1DM hoito ja seurannat ovat kehittyneet huomattavasti vuosien aikana, edelleen hyvän sokeritasapainon (HbA1c < 7%) saavuttaa vain noin 54%. Sikiön kannalta kehityksen riskialttein aika on alkuraskaudessa, jonka vuoksi on erittäin tärkeää suunnitella T1DM-äitien raskaudet etukäteen mahdollisten ongelmien ennaltaehkäisyn vuoksi.

Pitkäaikaisvaikutuksista T1DM-äidin lapsen terveyteen on hyvin vähän tutkittua tietoa ja tulokset ovat osin myös olleet ristiriitaisia. On kuitenkin löydetty viitteitä, että T1DM-äitien jälkeläiset olisivat todennäköisemmin merkittävästi ylipainoisia aikuisiässä ja kohonnut riski sairastua tyypin 2 diabetekseen. Lisäksi on havaittu, että nämä lapset käyttävät enemmän lääkityksiä, heillä on enemmän sairaalahoitojaksoja sekä kohonnutta kuolleisuutta lapsuusiässä verrattuna terveiden äitien lapsiin.

Tämän tutkimuksen tavoitteena oli selvittää, millaisia vaikutuksia äidin T1DM:lla on lasten myöhempään sairastavuuteen. Tutkimukseen osallistui 23 potilasta ja 23 kontrollia. Tutkimukseen osallistuneet T1DM-äitien lapset olivat pääsääntöisesti terveitä 9-10 vuoden seuranta-ajalla. Lapset syntyivät pienemmillä raskausviikoilla ja suurikokoisempina verrattuna kontrollilapsiin. T1DM-äitien lapsilla diagnosoitiin muutamia suku- ja virtsaelinten poikkeavuuksia ja hidastuvuutta näön kehityksessä. Kontrollilapsilla todettiin muutamia neurofysiologisia ongelmia, kuten aktiivisuuden ja tarkkaavuuden häiriötä (ADHD), jonka esiintyvyys tutkimuksessa oli jopa 14%. T1DM jälkeläisillä vastaavasti neurofysiologisia ongelmia ei todettu lainkaan.

Avainsanat: Tyypin 1 sokeritauti, raskaus, lasten sairastavuus

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1 INTRODUCTION

The number of people with type 1 diabetes (T1DM) in Finland is higher than anywhere else in the world. The number of T1DM patients has been increasing over the years (Diabetes, www.thl.fi), and T1DM is now the third most common autoimmune disease in Finland (Hänninen et al. 2017.). It is therefore described even as a national disease (Diabetes, www.thl.fi). Annually 350 Finnish T1DM women give birth, which is 0.6% of all Finnish childbirths (Vuori & Gissler 2013, Pallasmaa 2015). It has been expected that the number of new T1DM cases diagnosed before the age of 15 will double in the following decades, leading to a growing number of women at reproductive age to have long-standing T1DM (Harjusalo et al. 2008).

T1DM confers a significant additional obstetric risk associated with adverse perinatal outcomes. Increased rates of stillbirth, macrosomia, perinatal mortality, prematurity and operative delivery are observed in several national surveys. Rates of stillbirth and perinatal mortality among women with diabetes is still 3–5 times higher than in non-diabetic pregnancies. (Mackin et al. 2017)

Prenatal glycemic control remains suboptimal with only 54% of women having documented preconceptual HbA1c values and with 30% having hyperglycemic values leaning to elevated amounts of congenital malformations and pregnancy loss in diabetic pregnancies (Mackin et al 2017). The pregnancy of T1DM women should be well planned to achieve optimal outcome and during pregnancy it is crucial to maintain active glycemic management as well as monitoring of the status of possible diabetic complications (Kitzmiller et al 2008, Ringholm et al. 2012). In Finland pregnant women with T1DM are leaner than Finnish pregnant women on average (Vuori & Gissler 2013) and recommendations in T1DM pregnancy for HbA1c levels are <7% (Valle et al.2010). In addition, there has been no improvement in glycemic control among non-pregnant adults with T1DM since 1990's (Valle et al. 2010). In a Finnish population-based observational study made from 1988-2011, intensified follow-up and care before and during T1DM pregnancy, glycemic control improved markedly by mid-pregnancy even in women with the most severe DM complications. In all T1DM pregnant women HbA1c levels were increased (>7%) from prepregnancy to first trimester, but decreased systematically to <7% by midtrimester and remained there until delivery (Klemetti et al. 2015)

2 REVIEW OF LITERATURE

2.1 Pathogenesis and etiology of T1DM

T1DM is a chronic and progressive disease where autoimmune antibodies selectively destroy the pancreatic insulin secreting β-cells. Insulin enables glucose transportation into the cells. When circulating glucose uptake is hindered, hyperglycemia results. Without treatment chronic hyperglycemia results in the dysfunction of several organ systems, such as retinopathy, nephropathy, neuropathy, and various heart and vascular diseases. (Virkamäki & Niskanen 2010) The propensity for T1DM is inherent, though exposure to various environmental factors such as infections, nutritional agents, and factors affecting the gut microbiome may play a role (Ilonen 2004). The precise etiology and pathogenesis behind T1DM and its complications still remains unknown (Knip & Simell 2012).

2.2 T1DM and pregnancy

Since insulin was discovered in 1921, significant advances have been made in the management of type 1 diabetes (Casagrande et al. 2013). Prior to this discovery, maternal and fetal death were common (Pedersen 1977). Nowadays, fetal complications in T1DM pregnancies are mainly due to prevailing hyperglycemia (Visser & Valk 2014) leading to stillbirth, fetal macrosomia, and congenital malformations (Knorr et al. 2015). Maternal morbidity is increased because of developing or progression of previous diabetic complications (Tieu et al. 2017). For example, diabetic nephropathy during pregnancy increases the risk of pre-eclampsia to > 50% (Teramo & Kaaja 2011).

Fetal malformations in T1DM pregnancies mainly develop in gestational weeks 5-7, rendering later improvement in maternal glycemic control useless in this sense. In Finland, pregestational HbA1c of < 7% is considered adequate in the prevention of anomalies. (Teramo & Kaaja 2011)

In Finland, an early pregnancy ultrasound scan and early second trimester scan are available to all, and adequate for fetal screening in T1DM pregnancies, as well. With poor glycemic control in early pregnancy, an excess fetal cardiac sonography is recommended as structural cardiac malformations are the most common in T1DM pregnancies. Fetal well-being is monitored regularly form second trimester onwards. (Teramo & Kaaja 2011)

Risk of fetal asphyxia increases towards term pregnancy in T1DM pregnancies. Poor maternal glycemic control or fetal macrosomia increase the risk of fetal demise, e.g. via

decreased pulmonary maturation. Induction of labor or, in specific cases, an elective cesarean section are recommended. (Teramo & Kaaja 2011)

2.2.1 Pedersen hypothesis

Jorgen Pedersen, a Danish professor in internal medicine, introduced in 1977 a classic hypothesis of fetal overgrowth caused by increased placental transfer of glucose. Chronic hyperglycemia leads to hypertrophy of fetal pancreatic β-cells, hyperinsulinemia, and increased demand for glucose. (Pedersen1977) However, this hypothesis has also been negated since maternal HbA1c does not correlate with fetal macrosomia (Teramo et al. 1998).

2.2.2 White's classification system

Dr Priscilla White, an American pioneer, was among the first to investigate pregnancies of T1DM women. She noticed a variation in the prognosis of pregnancies of T1DM women. In 1949, she introduced a classification system for pregnant diabetic women according to the type of diabetes, age at onset and duration of the disease, and diabetic vascular complications. (White 1949, White 1965, Hare and White 1977)

Class	Age at Onset of Diabetes (yr)		Duration of Diabetes (yr)	Vascular Disease	Insulin Required
Gestational Diabetes					
A_1	Any		Any	No	No
A_2	Any		Any	No	Yes
Pregestational Diabetes					
B	> 20		< 10	No	Yes
C	10-19	or	10-19	No	Yes
D*	< 10	or	> 20	Yes	Yes
F (nephropathy)	Any		Any	Yes	Yes
R (proliferative retinopathy)	Any		Any	Yes	Yes
T (status post–renal transplantation)	Any		Any	Yes	Yes
H (ischemic heart disease)	Any		Any	Yes	Yes

Fig.1 Modified from Landon MB, Gabbe SG. Diabetes mellitus and pregnancy. Obstet Gynecol Clin North Am 1992; 19:633-54. Reproduced by permission.

2.2.3 Maternal glucose metabolism

In normoglycemic women, maternal glucose metabolism adapts progressively to optimize the flow of nutrients to the fetus, and fetal insulin secretion adapts to maternal glucose supply (Butte 2000, Hay 2006). Pregnancy creates a diabetogenic state even in normoglycemic women, and after a meal or a glucose stress test, the plasma glucose levels increase more than before

pregnancy. This diabetogenic effect remains most intense in the last trimester and insulin sensitivity decreases causing insulin resistance. (Teramo & Kaaja 2011)

In the first trimester of pregnancy the physiological sensitivity to insulin increases and the need for insulin actually decreases. As pregnancy proceeds to second trimester, the sensitivity to insulin contrarily decreases causing the need for insulin to double comparable to a prediabetic state in up to 66% of normoglycemic women. With an increased volume of maternal plasma, glucose passes the placenta easily and insulin resistance may further increase fasting hypoglycemia and post-meal hyperglycemia in the mother. (Virkamäki & Niskanen 2010) Since glucose passes through the placenta, fetal plasma concentrations are maintained at 0.5-1.0 mmol/l below maternal glucose concentrations until mid-pregnancy (Virkamäki & Niskanen 2010), leaving the fetus vulnerable to maternal hyperglycemia (Hay 2006). From gestational week 20 onwards fetal insulin secretion commences (Hay 2006). After delivery insulin sensitivity improves rapidly and the need for insulin reduces below the pre-pregnancy level and normalizes within a few weeks (Virkamäki & Niskanen 2010).

2.2.4 The placenta

Early pregnancy is a susceptible period for adverse insults to result in inadequate fetoplacental development. Oxidative stress causes disruptions in normal cellular signaling mechanisms leading in the leakage of reactive oxygen species (ROS). Mostly ROS are generated as a byproduct of mitochondrial oxidative metabolism. Oxidative stress occurs when there is an imbalance between antioxidant defense and ROS, and it affects cell behavior, differentiation, apoptosis, and other forms of cell damage (Halliwell et al. 1997). ROS are especially harmful for the developing fetus. Luckily, the placenta and the embryo develop in a low oxygen environment protecting the embryo from oxidative damage. However, in T1DM pregnancies hyperglycemia and inflammation increase the production of ROS and early pregnancy loss, pre-eclampsia, and fetal growth restriction are observed in T1DM pregnancies more often. These pathologies are influenced by early placental maldevelopment and oxidative stress. (Gauster et al. 2017)

By late first trimester, utero-placental blood flow is established and placental oxygen concentration escalates rapidly. Both early first term hypoxia and ROS burst due to the development of the placental vasculature, regulate normal placental morphogenesis and function. Changes in placental protein levels involved in oxidative and inflammatory processes have been observed during the first trimester of T1DM pregnancies, though the significance of this finding is unclear. (Gauster et al. 2017)

In T1DM pregnancies, placental morphology is abnormal with fibrinoid necrosis, villous immaturity, and chorangiosis compared to placentas in healthy pregnancies. The mechanism of developing placental abnormality remain unclear, though glucose deposits and inflammatory mediators are involved (Evers et al. 2003). However, vascular bed is involved in placental pathology as well since in T1DM pregnancies with nephropathy and pre-eclampsia fetal growth decelerates irrespective of maternal glycemic control (Teramo & Kaaja 2011). Intrauterine fetal death in T1DM pregnancies associates with low placental weight and placental abnormality (Crispi et al. 2018).

2.3 The fetus in T1DM pregnancies

2.3.1 Growth factors

Fetal growth is a complex process influenced by genetics, maternal factors, uterine environment, and maternal as well as fetal hormones. Both maternal and fetal growth factors are equally important (Langer 2000.) Human placental growth hormone (PGH) is found in the maternal circulation from gestational week 6 onwards. PGH replaces pituitary growth hormone (PTH) gradually during pregnancy and is affected by a direct autocrine and paracrine mechanism, or via the regulation of insulin-like growth factor 1 (IGF-1). (Kliman et al. 1986, Fuglsang et al. 2003). Maternal T1DM does not affect PGH concentrations during pregnancy. However, in T1DM women, maternal – but not neonatal – serum PGH concentrations correlate with fetal birth weight. (Higgins et al. 2012). Serum PGH concentrations are higher in infants of pre-eclamptic women, and maternal PGH is speculated to prevent fetal growth restriction (Mittal et al. 2007).

The IGF hormones have both mitogenic and anabolic effects (Sara & Hall 1990) in human development through two IGF peptides (IGF-1 and IGF-2), six IGF binding proteins (IGFBPs) and several IGFBP proteases (Higgins & McAuliffe 2010). The binding proteins regulate the bioavailability and biological activity of both IGFs (Higgins & McAuliffe 2010). IGF-1 levels are regulated by circulating glucose concentrations through a negative feedback system. In T1DM women, serum IGF-1 concentrations are decreased during pregnancy, whereas newborn umbilical cord serum concentrations are increased (Whittaker et al. 1990, Higgins et al. 2012). Both fetal IGF peptides are crucial for fetal growth since IGF-1 has a positive and IGFBP1 a negative correlation with birth weight in both term and preterm newborns(Higgins & McAuliffe 2010).

IGF-1 increases with gestational age. Cord blood IGF-1 concentrations are increased in macrosomic infants of both pregestational diabetic and normoglycemic women compared to normosomic newborns. Fetal IGF-1 correlates with aortic intima media thickness, and may influence the atheroschlerotic process later in life since it correlates with neonatal cord serum HDL cholesterol concentrations. IGF-2 promotes differentiation of cells by endocrine and autocrine means, and correlates with placental weight, but not birth weight. In T1DM pregnancies, cord serum IGF-2 concentrations are increased compared to healthy controls. (Higgins & McAuliffe 2010)

IGFBP1 sequesters IGF and regulates its availability in circulation minute–by–minute. It is directly regulated by insulin, cortisol, and glucagon. IGFBP1 serum concentrations increase during pregnancy and may reflect placental function. In T1DM pregnancies, the feedback system in IGFBP1 production is disrupted and the maternal IGFBP1 concentrations are increased. (Higgins & McAuliffe 2010)

IGFBP3 is the predominant maternal serum IGF binding protein. It has a high binding affinity for IGFs, binding up to 70-80% of total serum IGF-1 and IGF-2. Bound IGFBP3/IGF complexes act as a reservoir of circulating IGF. Cord IGFBP3 concentrations are increased in infants of T1DM mothers (Holmes et al. 1999), as well as in T1DM mothers too (Higgins et al. 2012).

Adiponectin is produced exclusively by adipose tissue. Its´ expression is negatively controlled by fat tissue. Adiponectin regulates insulin sensitivity inversely: high concentrations decrease insulin resistance. It stimulates fatty acid oxidation, reduces plasma triglycerides, improves glycemic control, and contributes to the prevention of metabolic syndrome. No correlation with markers of adiposity exist. (Higgins & McAuliffe 2010)

Normally, leptin is secreted by adipocytes. During pregnancy, the placenta produces leptin with 95% delivered to maternal plasma. Leptin stimulates energy expenditure and suppresses appetite, and increased concentrations are observed in obese and women due to body fat content and reproductive hormone concentrations. Cord blood leptin concentrations are increased in female infants compared to males and correlate with birth weight, birth weight SD score, placental weight, and HDL cholesterol concentrations in infants. Maternal plasma leptin concentrations in T1DM and healthy control pregnancies are similar, but fetal and placental leptin concentrations are increased in infants of diabetic mothers. Furthermore, umbilical leptin concentraions are increased in diabetic pregnancies with fetal macrosomia. (Higgins & McAuliffe 2010)

2.3.2 Placenta and fetal growth restriction

Intrauterine growth restriction (IUGR) is a failure to achieve fetal endorsed growth potential and affects about 7-10% of normal pregnancies. IUGR is determined when fetal growth is under – 2 standard deviation (SD) scales. The main cause is placental insufficiency leading to fetal undernutrition, hypoxemia, and pressure or volume overload of the fetal cardiovascular system (Crispi et al. 2018).

2.3.3 Congenital abnormalities

Maternal hyperglycemia is a teratogen during fetal development (Ornoy et al. 2015). As previously stated, hyperglycemia and ensuing inflammation in T1DM pregnancies increase the production of ROS, resulting in cell death or fixation of genome mutations in the fetus, and disturbances in fetal organ maturation (Moreli et al. 2014). Oxidative stress induces protein oxidation, lipid peroxidation, and damage in both mitochondrial and nuclear DNA. Since cells have a certain potential to repair mutations, the changes in DNA evidentially affect not only the development of the fetus, but the long-term health of the offspring too. Furthermore, maternal hyperglycemia affects the production of fetal blood cells, mononuclear cells in specific. (Moreli et al. 2014)

Major anomalies in T1DM pregnancy occur as a result of metabolic disturbances in the first trimester. Poor glycemic control of T1DM before conception and during the first trimester associate with major birth defects in 5-10% and spontaneous abortion in 15-20% of pregnancies. Hyperglycemia affects various organs during active organogenesis. Though most of the anomalies develop during the first trimester, the developing brain is susceptible throughout pregnancy, as the major developmental events of the cerebral cortex occur during second trimester and early postnatal period. (Ornoy 2003, Ornoy et al. 2015)

Central nervous system	Cardiovascular system	Craniofacial structures
Anencephaly	Hypoplastic left or right heart syndrome	Hemicranial microsomia
Acrania	AVSD and VSD	Microtia
Meningomyelocele	Tricuspid atresia and mitral atresia	Micrognathia
Microencephaly	Double inlet left ventricle	Micro ophthalmia
Exencephaly	Double outlet right ventricle	Frontal nasal dysplasia
Holoprosencephaly	Transposition of the great arteries	Lens opacity
Spina bifida	Tetralogy of Fallot	Cleft lip/palate
Arrhinencephaly		

Fig.2 Major congenital anomalies in offspring of T1DM mothers. (Adopted from Ornoy et al. 2015)

2.3.4 Fetal organ maturation

Maternal T1DM affects fetal organ maturation. Changes in fetal immunologic responses are observed during pregnancy, and there seems to be an ongoing interaction between the maternal and fetal immune systems (Warncke et al. 2017). Furthermore, delayed fetal lung maturation is observed in T1DM pregnancies as well (Moore 2002).

2.3.5 Cardiomyopathy

Cardiomyopathy of various severity is observed in up to 40% of infants born to T1DM mothers. Cardiomyopathic changes may affect fetal cardiovascular function and predispose the fetus to hypoxic insults (Lisowski et al. 2003, Russell et al. 2008 a&b). Some studies have associated cardiomyopathy with maternal glycemic control, others have not (Gandhi 1995, Tshiyombo & Oulton 2001, Russel et al 2008a). 5% of cardiomyopathic infants develop outflow tract obstruction and congestive heart failure (Russell et al. 2008b). Usually cardiomyopathy dissolves in the first weeks after birth and ultrasound findings disappears during the first six months (Hay 2011).

2.3.6 Fetal macrosomia

Multiple factors are involved in the imbalanced fetal growth of T1DM women with main focus on insulin and the IGF family, glucose, leptin and adiponectin (Ornoy et al 2015). In T1DM pregnancy, fetal bodies are larger due to the accumulation of subcutaneous fat, liver and muscle mass, with a normal-sized head and brain (Teramo 1998, Naeye 1965). In normoglycemic pregnancies, fetal macrosomia is usually symmetrical since it is caused by genetic factors, placental function, and maternal nutrition (Teramo et al.1998).

To evaluate growth, fetal measures are compared to a SD-scale adjusted for gestational age, fetal gender, and sometimes ethnic backround as well. The measurements from control pregnancies are given a mean value of 0. Above and below 2 SD rates growth is determined as fetal macrosomia (large for gestational age, LGA) or small for gestational age (SGA). (Pihkala et al. 1989). Fetal macrosomia associates with obstetric and perinatal complications, such as fetal demise, instrumental delivery, shoulder dystocia, birth trauma, chronic fetal hypoxia, birth asphyxia, and obesity in later life (Jaffe 2002, Teramo 2010, Hay et al.2012). Macrosomic fetuses are monitored every 1-4 weeks at an outpatient clinic in Finland (Saarikoski 2016).

2.3.7 Fetal hypoxia

In pregnancy, fetal circulating oxygen and carbon dioxide levels depend on placental function, where the transfer of gases occurs (Brander & Varpula 2014). Placental insufficiency predisposeses for a limited oxygen delivery capacity and fetal hypoxemia. Fetal circulation is redistributed with continuous flow to vital organs (brain, heart, adrenals) at the expense of peripheral tissues and fetal growth. Oxygen deficiency leads to metabolic acidemia, and can be measured from fetal scalp or umbilical cord arterial blood samples directly. Without improvement in the placental oxygen delivery, fetal carbon dioxide concentrations accumulate and the fetus becomes 10cademic. Metabolic acidemia occurs when the transfer of gases is insufficient and circulatory compensation mechanisms fail. Birth related hypoxemia, accumulation of carbon dioxide, and circulatory defiency in tissues causing hypoxia is called asphyxia. The commonly used definition of newborn asphyxia is based on both the poor general condition and the metabolic acidosis found in blood samples. (Fellman & Luukkainen 2016 (b))

The risk for fetal hypoxia is significant in T1DM pregnancies (Madsen & Ditzel 1984) since fetal hyperglycemia and hyperinsulinemia increase fetal basal metabolic activity and oxygen consumption. Also, oxygen delivery capacity is limited due to placental insufficiency. (Phillips et al. 1984, Milley et al. 1986, Teramo et al. 2004b)

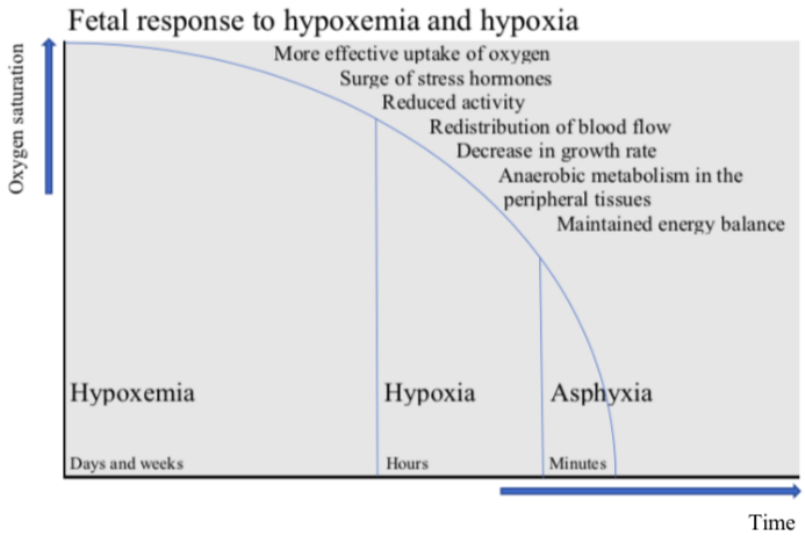

Fig.3 Fetal response to hypoxemia and hypoxia. (Adopted from Madsen & Ditzel 1984, Escobar et al. 2013, Brander & Varpula 2014)

Fetal susceptibility to hypoxemia has caused the need to find reliable methods to detect fetal hypoxemia. Erythropoietin (EPO) production is triggered by tissue hypoxia. In fetuses elevated levels of amniotic fluid EPO are seen in anemic and hypoxic fetuses, though the response to produce EPO is less pronounced than in adults (Halvorsen & Bechensteen

2002). In T1DM pregnancies, elevated umbilical cord serum and amniotic fluid levels of EPO are observed (Teramo 2010) and associate with fetal macrosomia, obstructive cardiomyopathy and neonatal hypoglycemia (Teramo et al. 2004a&b). However, the severity of hypoxia is not reflected in EPO levels (Turner et al 2016). Other triggers for EPO production exist, and hyperinsulinemia and oxidative stress among predisposing factors for EPO stimulation in T1DM pregnancies as well (Todorov et al. 2000).

2.4 Perinatal complications in T1DM pregnancy

2.4.1 The Apgar score

After birth neonatal wellbeing and prognosis is assessed by appointing marks upon performance on respiration, pulse, activity (muscle tone), grimace (reflex irritability), and appearance (skin color). Apgar points are evaluated at 1 and 5 minutes after birth. Umbilical artery sample is used among Apgar rating system, and the pH of the blood sample is valued as normal when > 7.14. (Luukkainen 2011)

THE APGAR SCORE

MNEMONIC	0 POINTS	1 POINTS	2 POINTS
Appearance	blue or pale	blue extremities pink body	body and extremities pink, no cyanosis
Pulse	absent	< 100 beats per minute	>100 beats per minute
Grimace	no response to stimulation, floppy	grimace on suction or aggressive stimulation	cry on stimulation
Activity	none	some flexion of arms and legs	active flexion against resistance
Respirations	absent	weak, irregular and slow	strong crying

Fig 4. Modified from A proposal for a new method of evaluation of the newborn infant. APGAR, V. Curr Res Anesth Analg. 1953 Jul-Aug;32(4):260-7. Reproduced by permission.

Marks of neonatal wellbeing have a certain value in the Apgar rating system and are used to estimate fetal birth asphyxia. 1-minute Apgar points >3 predict good prognosis . Mortality in severe asphyxia is 10-25% and the risk of suffering permanent organ damage if remained alive is 10-30%. (Fellman & Luukkainen 2016 (b)) According to most studies, 5-minute Apgar evaluation is more accurate for long term prognosis. (Ehrenstein et al. 2009)

Birth asphyxia	Apgar rate (1 min)	Umbilican artery sample (pH)
Mild	4–6	< 7.16
Moderate	< 6	< 7.0
Severe	0–3	< 7.0

Fig 5. Values of fetal birth asphyxia. (Adopted from Fellman & Luukkainen 2016 (b))

2.4.2 Preterm birth complications

Preterm birth is defined as birth before gestational week 37 and a very premature birth before gestational week 28. They associate with multiple neonatal problems. Neonatal mortality is inversely proportional to the duration of the pregnancy and is highly affected by organ immaturity. (Fellman and Luukkainen, 2016 (a))

The prognosis of the preterm newborn is affected by the degree of brain damage, bronchopulmonary dysplasia and respiratory distress, low birth weight, gastrointestinal problems, and retinopathy of prematurity. Respiratory problems are caused by immaturity of the lungs and the lack of surfactant production resulting in respiratory distress syndrome (RDS). Antenatal corticosteroids to mature fetal lungs are administered to the mother when preterm birth is imminent (Kaypahoito.fi 2018). Other complications include pathological hyperbilirubinemia caused by increased haemolysis, hypotension, and metabolic disturbances such as hypoglycemia, hypocalcemia and hypomagnesemia. (Fellman & Luukkainen, 2016)

Most of preterm deliveries are either induced or by caesarean section due to obstetric complications. Maternal T1DM per se does not increase the risk of preterm birth, but the risk of obstetric complications is increased. Maternal hyperglycemia attenuates the complications of the preterm infant. (Fellman & Luukkainen, 2016)

2.4.3 Neonatal hypoglycemia

The most common reason for neonatal intensive care unit (NICU) stay in T1DM pregnancies is neonatal hypoglycemia (blood glucose <2.6 mmol/l) during the first neonatal days (Maayan-Metzger et al 2009). After birth, maternal glucose supply abruptly stops leading to infant hypoglycemia. Simultaneously, infant insulin production remains high, glycogenolysis is decreased, and there is a lack of alternate substrates, such as free fatty acids or ketone bodies (Hay 2011). Luckily, this period of neonatal hypoglycemic hyperinsulinemia is swiftly reversed. In the Finnish healthcare, the newborns of T1DM mothers are carefully monitored

and treated. If necessary, intravenous glucose treatment is administered for 1–2 days (Fellman & Luukkainen 2016).

2.4.4 Respiratory disorders

Respiratory problems, such as transient tachypnea, respiratory distress syndrome (RDS) and pulmonary hypertension, are common in the neonates of T1DM women (Robert et al. 1976). Both hyperglycemia and hyperinsulinemia may delaye fetal lung development and increase the incidence of RDS (McGillick et el. 2014). Pneumocyte production of surfactant is inhibited by hyperglycemia in the fetus (Gewolb & O'Brien 1997). The number of preterm births of T1DM women contribute to the frequency of RDS, though maternal T1DM is an independent risk factor as well (Robert et al. 1976). Hyperviscosity due to polycythemia and chronic fetal hypoxia may induce pulmonary hypertension. Furthermore, an elective cesarean section without labor-induced stress increases neonatal transient tachypnea (Hay 2011).

2.4.5 Fetal hyperbilirubinemia

Hyperbilirubinemia is caused by hemolysis, usually occurring on the second postnatal day. It is defined pathological when it commences on the first postnatal day or continues for a week in a term neonate or two weeks in preterm neonate, or serum bilirubin concentrations exceed 85 µmol/l/day. Hemolytic disease is the most common cause for early onset pathological hyperbilirubinemia. Hyperbilirubinemia occurring after two weeks of birth is usually non-pathological and caused by breastfeeding. Pathological cases are treated with blue light therapy, which changes the structure of unconjugated bilirubin to a water-soluble urine-secreted photoisomer. (Fellman & Luukkainen, 2016)

2.4.6 CNS development

Neurodevelopmental studies on offspring of T1DM mothers show an increased rate of attention deficit hyperactivity disorder (ADHD), learning difficulties, and possibly autism spectrum disorders (Ornoy et al. 2015). Lower cognitive function in adolescent offspring of T1DM women is reported (Bytoft et al. 2016). Underlying mechanisms are thought to involve increased oxidative stress, hypoxia, apoptosis, and epigenetic changes caused by the hyperglycemic environment (Ornoy et al. 2015).

2.5 Long term complications in the offspring of T1DM women

Knorr et al (2015) examined perinatal mortality, hospital admissions, medication, and their relations to maternal HbA1c in the offspring of T1DM women. A higher incidence in offspring mortality was found from circulatory and genitourinary diseases and perinatal disorders as leading causes of death. No association between maternal glycemic control and neonatal mortality were observed. Perinatal disorders associated with higher incidence of death during the first year of life. Furthermore, in all age groups until the 15th year, the offspring had more hospital admissions for infections, endocrine diseases, perinatal disorders, congenital malformations, and unspecified diseases. These correlated consistently with maternal pregestational and first trimester HbA1c levels. However, no association between maternal HbA1c and the incidence of congenital malformations were seen in the offspring of T1DM women. Additionally, the use of medication for alimentary tract and metabolism, systemic hormones, infection, musculoskeletal system, nervous system, respiratory tract system, and sensory organ related disorders was increased and associated with maternal HbA1c levels. Knorr concluded that maternal T1DM leads to short- and long-term health problems in the offspring.

3 AIMS AND METHODS

The aim was to find out how maternal T1DM affects the offspring later health. A study on 40 T1DM and 100 healthy pregnant women during 2006-2009 at University of Turku was performed. Ultrasonographic measures and post-partum samples were collected of placental and umbilical cord blood samples, as well as maternal sera during pregnancy. The Ethics Committee in the Hospital Districts approved the research protocol (license 167/2005 §183). For this study, we compared 23 T1DM and 23 control mothers and offspring at 9-10 years of age to observe differences in offspring later health.

4 RESULTS

The T1DM women mostly used human insulin (Protaphane ©) or glargineinsulin (Lantus ©) as long-term insulin, though a few had insulin pumps with short-term insulin. 30% accumulated further diabetic complications with proliferative retinopathy, diabetic nephropathy and vascular disease. The HbA1c level decreased from 7.4% (gestational week 7-9) to 6.5% (gestational week 33-40). Ceaserean section rate was 48% with majority performed due to fetal macrosomia.

55% of ceaserean sections were elective and 45% acute. 52% delivered vaginally, with half being spontaneous and half labor-induced. Majority of the inductions were for fetal macrosomia, with a third converted to ceaserean sections.

In the control group, only 3 delivered via cesarean section. 25% of deliveries were induced with indications such as pre-eclampsia, hepatogestosis, fetal macrosomia and gestational age of 42+1.

Table 1. Maternal characteristics

Variable	**T1DM**	**Control**
N	23	23
Maternal age (years)	29.5	28.5
Prepregnancy BMI (kg/m2)	26.7	25.0
Duration of pregestational diabetes (years)	14	
Long term insulin		
Human insulin (Protaphane ©)	56.5% (13)	
Glargineinsulin	30.4% (7)	
Short term insulin		
Lisproinsulin (Humalog ©)	69.6% (16)	
Aspartinsulin (Novorapid ©)	30.4% (7)	
Insulin pump		
Lisproinsulin (Humalog ©)	4.3% (1)	
Aspartinsulin (Novorapid ©)	8.7% (2)	
White class (prepregnancy)		
A		4.3% (1)
B	17.4% (4)	
C	26.0% (6)	
D	34.8% (8)	
R	13.0% (3)	
F	4.3% (1)	
F+R	4.3% (1)	
White class increased during pregnancy	30.4% (7)	
HbA1c% gestational week 7-9	7.4%	
HbA1c% gestational week 33-40	6.5%	5.4%

In the T1DM group, 96% of neonates were treated in NICU for approximately 4 days, with one newborn monitorized for >30 days. Causes of admittance were hypotonia, difficulties in ventilation, and hyperbilirubinemia (approximately 2 treatments per patient). 91% of the NICU admitters received glucose-infusion for approximately 2.4 days. In the control group, 5 neonates were admitted to NICU with an average of 6 days treatment. Causes of admittance were difficulties in ventilation, hypoglycemia and chorioamnionitis. 60% of the NICU patients received light treatment to hyperbilirubinemia (average of 1.3 treatments).

Ultrasonographic examination of neonatal heart, kidneys and brain was performed for all in the T1DM group. Three cardiac murmurs, one septal hypertrophy and 3

kidney abnormalities were found. Three of the control offspring had cardiac murmurs in later childhood.

Later in childhood, genital abnormalities were found in three males of T1DM mothers. A cryptorchid, imperfect closing of the foreskin, and a micropenis were diagnosed. Three of the offspring in the T1DM group had vision impairments, with heterophoria, myopia, and delayed development of vision. In the control group three children were diagnosed with ADHD.

Table 2. Offspring characteristics

Variable	**T1DM**	**Control**
Gender		
Male	47.8% (11)	56.5% (13)
Female	52.2% (12)	43.5% (10)
Gestational week at birth	37+2	39+2
Delivery		
Vaginally	52.2% (12)	87.0% (20)
Spontaneous	50.0% (6)	65.2% (15)
Induced	50.0% (6)	25.0% (5)
Fetal macrosomia	88.9% (8)	20.0% (1)
Mothers preeclampsia	11.1% (1)	40.0% (2)
Hepatogestosis		20.0% (1)
Gestational age 42+		20.0% (1)
Vacuum extraction	16.7% (2)	10.0% (2)
Induction changed to ceaserean section	33.0% (3)	
Ceaserean section	47.8% (11)	13.0% (3)
Elective	54.5% (6)	33.3% (1)
Acute	45.5% (5)	66.7% (2)
Crash		
Indications		
Fetal macrosomia	72.7% (8)	
Maternal diabetic complications	9.0% (1)	
Maternal narrow pelvis	9.0% (1)	
Fetal CTG complications	9.0% (1)	
Apgar (1min)	7.4	8.4
Apgar (5min)	8.4	8.7
Arterial pH	7.27	7.35

Table 3. NICU

Number of treated	95.7% (22)	21.7% (5)
Days	4	6
Cause of admittance		
Hypotonia	50.0% (11)	40.0% (2)
Dopamine support	27.0% (3)	
Difficulties in ventilation	40.9% (9)	60.0% (3)
Hyperbilirubinemia	40.9% (9)	60.0% (3)
Treatments	2.2	1.3
Hypoglycemia	90.9% (20)	40.0% (2)
Glucose infusion	100% (20)	100% (2)
Days of infusion	2.4	3.0
Treated with antibiotics	45.5% (10)	80.0% (4)
Days of treatment	4.2	7.5
Ultrasonographic scanning	100.0% (23)	17.3% (4)
Cardiac murmur	13.0% (3)	13.0% (3)
Septal hypertrophy	4.3% (1)	
Kidney abnormalities	13.0% (3)	
Genital abnormalities	13.0% (3)	
Males	100.0% (3)	
Females		
Vision impairments	13.0% (3)	
Bedwetting		8.7% (2)
ADHD		13.0% (3)

5 CONCLUSIONS

The main finding of this study was, that the offspring of T1DM women were mainly healthy at 9-10 years of age. Born more premature and macrosomic, the newborns of T1DM women were extensively monitored and neonatal problems were solved rapidly after delivery. Cardiac dysfunction did not cause problems beyond the neonatal period, though observations from later life are absent. Some genito-urinary malformations and vision developmental delays were reported mainly in male offspring. Curiously, a few cases of neuropsychological ADHD were diagnosed in the control offspring. The prevalence of ADHD is estimated to be up to 14% of children and adolescents (Davidovitch 2017), more surprising is the lack of reported ADHD type neuropsychological disorders in the T1DM offspring.

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