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Maternal Diabetes and the Consequences for her Offspring

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Abstract

In pregnancy, there is an inevitable sharing of maternal nutrients through transport via the placenta. Changes in the maternal system affect the fetal plasma composition and thus the development of fetal organs. Alterations in the fetal environment that affect fetal development have been hypothesized to have consequences in postnatal life. Maternal diabetes, which is associated with high blood glucose levels (hyperglycemia), is one such compromising environment; excess glucose is shunted into the fetal system which then must make adaptations to the altered environment. This results in a variety of fetal, neonatal, and postnatal consequences for the offspring of diabetic mothers including very large size at birth, birth defects, various short-term and long-term complications, and harmful effects on the brain. This review is aimed at summarizing the effects of maternal diabetes on her offspring, with a focus on long-term effects in the brain. Neuropsychological deficits in intelligence and memory, psychomotor development and sensory functions, as well as attention and hyperactivity, have been shown to be associated with maternal diabetes in the literature. However, with tightly controlled blood glucose levels, these outcomes have the potential to be minimal consequences of maternal diabetes. Unfortunately, some segments of the population do not have adequate control of their blood sugar level, and are still exposed to effects of hyperglycemia. One such population is our First Nations people who have experienced epidemic-like increases in type 2 diabetes in the past 20 years. Due to barriers in treatment of this population, they are still at risk for the more severe consequences of uncontrolled diabetes, including those consequences for infants born to diabetic mothers. There has been both a national and an international drive to find solutions to this problem, as well as a critical look into treatments and prevention regimes, for the general population and for Aboriginal populations.

Fetal/Maternal Relationship: Normal Pregnancy

Pregnancy is a state that allows a life form to develop with the support and protection of its mother's body. The growth and development of the fetus in gestation is partially determined by the genome of the fetus, which produces its own growth factors as well as the majority of its hormones. However, this genetic influence is highly dependent upon interaction with environmental factors (Van Assche, Holemans & Aerts, 2001). One environmental factor vital in the growth and development of the fetus is nutrition. The fetus is solely dependant on the mother to supply its nutrients. It is also dependent on the placenta, an essential organ in pregnancy, to transfer these nutrients from the maternal system to its own. Thus the fetal nutrition is a reflection of that of the mother's. This interaction exists in a sensitive equilibrium; if disturbed, there are fetal developmental consequences (Van Assche et al., 2001).

Changes in the plasma nutrient levels in the maternal system have an effect on the fetal plasma composition, and thus affect organogenesis in the fetus. This altered metabolic condition has an influence on the maturation of all organs, including, but not limited to, the heart, gastrointestinal tract, pancreas, and brain. This potential for long-term physiological alteration is due to that fact that 43 of the 48 cell division cycles of life occur between conception and the birth of a new being, indicating that the majority of development and programming of the bodily systems occurs before birth (Van Assche et al., 2001). Thus fetal life, and all of the developmental processes that occur during this stage, are fundamentally important in the life outcomes of the future individual.

The adaptations made by the fetus in sub-optimal intra-uterine environments create consequences for its long-term health. This has been referred to as the 'fetal origins of adult disease', a term coined by Barker in 1993 (Barker et al., 1993). In this hypothesis he states that the physiological, neuroendocrine or metabolic adaptations made by the fetus to periods of intra-uterine environmental alterations result in non-optimal programming of the developmental pattern of proliferation and differentiation of fetal organs and tissue, if it occurs during critical periods in the development of these organs (Edwards, Coulter, Symonds & McMillen, 2001). This topic has been the focal point of much research, with a focus on the negative outcomes (Lampl & Jeanty, 2004). There is evidence that a diabetic intra-uterine environment may be one such sub-optimal environment for the growth and development of the fetus, and thus is proposed to have consequences in later life (Van Assche et al., 2001). The proliferation of adipocytes, pancreatic beta cells, and muscle cells in the fetus are critical for development and occur during

the third trimester (last three months) of pregnancy. Abnormalities of proliferation of these types of cells in the fetus in the maternal diabetic intra-uterine environment may result in long-term effects ranging from neurological and psychosocial impairment to the development of metabolic and cardiovascular disease in the adult (Carrapato & Marcelino, 2001; Carrapato, 2003). Not only does diabetes have an effect in the intra-uterine environment, it also may influence growth rates in neonates that are breast-fed by diabetic mothers, since infants retain some programming vulnerability for a short period after birth. This has been shown by Holemans et al. (1999) in streptozotocin-diabetic rats in a cross-fostering experiment. In this experiment, neonates born to non-diabetic rats were suckled by either their non-diabetic mother, or a streptozotocin-diabetic rat. The authors showed that there was a trend towards lower adult body weight in both those offspring born to streptozotocin-diabetic mothers, and those suckled by them. Thus programming may continue for a short time after birth, since the neonate is still dependant on the still deficient mother for nutrients, in the form of lactation (Holemans et al., 1999).

What Is Diabetes?

Diabetes is a chronic disease that has no cure, and is one of the leading causes of death in Canada (Canadian Diabetes Association, n. d.; Public Health Agency of Canada, 2005). The prevalence is on the rise worldwide (Lampl & Jeanty, 2004). In the Canadian population of approximately 32 million, diabetes affects more than two million. However, by the end of the decade, this number has been predicted to rise to three million. Overall diabetes is a contributing factor in the deaths of approximately 41,500 Canadians each year. Heart and stroke is the leading cause of death in diabetes; it accounts for approximately 80% of death of people with diabetes. Diabetes has costs both for the afflicted person, and the general population. Compared to a person without diabetes, a diabetic person incurs medical costs that are two to three times higher, and they also face direct costs for medication and supplies ranging from $1,000 to $15,000 a year (Canadian Diabetes Association, n.d.).

Diabetes is a disease in which the body is not able to either produce or properly use insulin. Insulin is a hormone that is required for the conversion of glucose into energy within the cell. The production of insulin occurs in the pancreas, within a specific cell type, the beta cells of the islets of Langerhans. As glucose enters our blood, from the consumption of food, the pancreas automatically produces the appropriate amount of insulin to transfer this glucose into cells. Insulin in the blood circulation then binds to

glucose receptors on the cell surface, opening them, and allowing glucose to enter. Once in the cell, glucose is used in cellular metabolism, and energy production. If glucose does not enter the cell, either because there is no insulin to open the glucose channel, or if there is a problem with the action of insulin (usually there is a problem after glucose binds to the receptor), glucose remains in the blood. High glucose levels in the blood are associated with two major problems; cellular energy starvation and damage to tissue and organ system, for example eyes, kidneys, brain, nerves or heart (Silverthorn, 2001).

There are three general classifications of diabetes: 1) Type 1 or insulin dependent, 2) Type 2 or insulin independent and 3) Gestational. Each classification is associated with a unique etiology. Type 1 (insulin dependent) diabetes, previously known as juvenile diabetes, is the result of the body's failure to produce insulin. It accounts for 10% of all diabetes cases. In this form of diabetes the beta cells of the pancreas are destroyed. This is thought to be an autoimmune response since antibodies which target these cells have been found within a portion of the type 1 afflicted patients (Diabetes Mall, Health Through Information). Type 2 (insulin independent diabetes) accounts for most of those diagnosed with the pathology. Patients with type 2 diabetes usually have insulin resistance in combination with a relative insulin deficiency due to a reduced number of pancreatic beta cells. The third type of diabetes affects approximately 4% of all pregnant women who have never before had diabetes, but who do have high blood glucose levels during pregnancy. It is referred to as gestational diabetes. It occurs because hormones produced by the placenta to aid in fetal development block the action of the mother's insulin in her body, thus causing insulin resistance. Fortunately, this is a transient form of diabetes, and it disappears shortly after the birth of the baby. However, women who experience gestational diabetes are more prone to type 2 diabetes later in life. Approximately 3.5% of non-Aboriginal women and up to 18% of Aboriginal women will develop gestational diabetes (Canadian Diabetes Association. Aboriginal Section, n.d.).

Although diabetes is a worldwide problem, as are its consequences, there is no internationally accepted protocol to diagnose it in the general population, nor that of the gestational population. Depending on the country and purpose of the evaluation, different methods are used, for example different ranges of acceptable blood glucose levels. The World Health Organization (WHO) has a diagnostic criteria for diabetes which are based on a 2-hour 75g oral glucose tolerance test. If either the fasting glucose level is greater than 126 mg/dL or the 2-hour glucose level is greater than 140 mg/dL, gestational

diabetes is diagnosed. This method is used in most countries outside of North America (Setji, Brown & Feinglos, 2005). The American Diabetes Association uses different diagnostic criteria. The diagnosis of diabetes is given if two tests, performed on two different days, confirms the following: i) a random plasma glucose level of 200 mg/dL and presence of other diabetes symptoms, ii) a fasting plasma glucose level of 126 mg/dL, taken after an 8 hour fast, or iii) 2-hour plasma glucose level of 200 mg/dL during 75-g oral glucose tolerance test. Gestational diabetes is diagnosed with slightly altered criteria, where a 100-g oral glucose tolerance test is used to screen for plasma glucose levels in unsafe elevated levels (American Diabetes Association, 2003; 2006). In Canada we adhere to the new diagnostic criteria put forth by the Canadian Diabetes Association (CDA), which are based on a revision made in 1998. These new criteria are based upon recent studies that claim that the previous diagnostic criteria, which used the fasting plasma glucose test lacked sensitivity when compared to the oral glucose tolerance test. The oral glucose tolerance test, however, is less specific and lacks test-retest reliability. Therefore a new fasting plasma glucose diagnostic criterion has been introduced in which the sensitivity has been increased by lowering the cut-off point for a diagnosis of diabetes, from 7.8 to 7.0 mmol/L (Public Heath Agency of Canada). Gestational diabetes tends to be diagnosed around 28 weeks of pregnancy, though there is no evidence that this is the optimal time for diagnosis. The American Diabetes Association (2003; 2006) recommends that risk assessment for gestational diabetes be undertaken at the first prenatal visit. High risk women should be tested as soon as possible thereafter. High risk women not found to have gestational diabetes at the first visit should be tested again between 24 and 28 weeks of gestation (American Diabetes Association, 2003; 2006). The Canadian Diabetes 2003 *Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* recommend "that all women be screened between 24 and 28 weeks of gestation using a glucose tolerance test. For women at high risk, the testing should be done during the first trimester, then again during the second and third trimesters, even if the first test is negative." Risk factors for the development of gestational diabetes includes history of gestational diabetes, obesity, glucose intolerance, and a family history of type 2 diabetes (Setji et al., 2005).

Mechanism By Which Diabetes Influences Development In The Fetus

In general, pregnancy, even those in non-diabetic mothers, is a diabetogenic condition for the mother since it is characterized by alterations in hormone states, insulin resistance, and hyperinsulinemia due to a compensatory pancreatic beta cell response. This is due to the requirement of the maternal

system to not only provide metabolic fuel for itself, but also for the energy needs of the fetus the mother is carrying. At the beginning of the second trimester, maternal insulin sensitivity is reduced by up to 80%. The occurrence of this is responsible for the concentration dependent shunting of nutrients to the fetus, which is required for its adequate growth and development. The pregnant woman is therefore forced to use lipids, as opposed to glucose, in cellular metabolism. Since the maternal insulin cannot transcend the placenta, the metabolism of these nutrients by the fetus is dependent on the fetal production of insulin (Setji et al., 2005; Ter Braak, Evers, Erkelens & Visser, 2002).

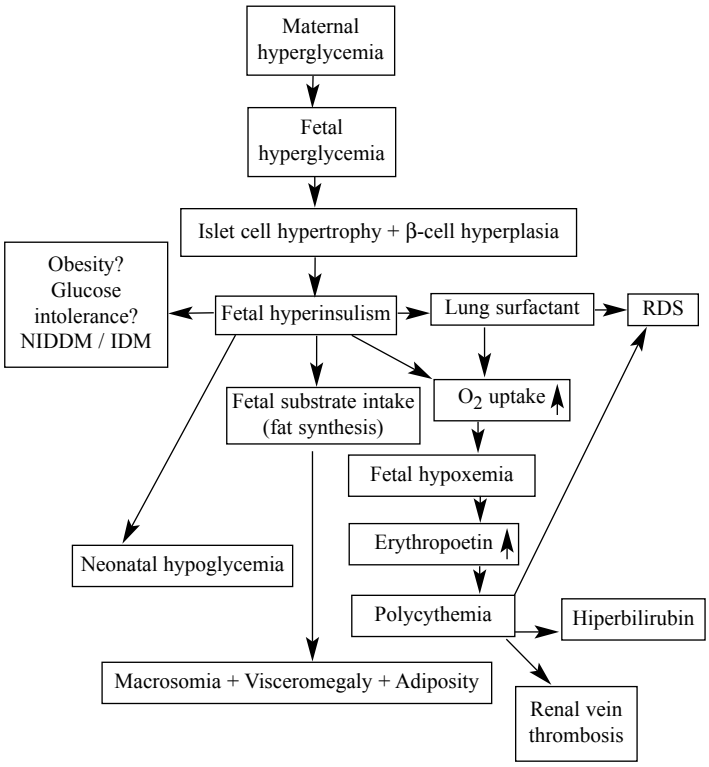
In the case of gestational diabetes, there is a greater severity of insulin resistance compared to the insulin resistance seen in normal pregnancies (Setji et al., 2005). This results in increased levels of glucose transported across the placenta to the fetus, thus maternal hyperglycemia is fetal hyperglycemia (Lampl & Jeanty, 2004). It should be pointed out that treatment of hyperglycemia with insulin is associated with an increased risk of severe hypoglycemia (Setje et al., 2005). Clinical studies have not established an association between maternal hypoglycemia and abnormal fetal development, although animal studies indicate that hypoglycemia can cause birth defects. It has been proposed that hypoglycemia resulting from a large maternal insulin response may cause neural defects, as well as other central nervous system defects in the fetus (Ter Braak et al., 2002). Clinical studies indicate that maternal diabetes mainly results in fetal maacrosomia (i.e., fetal overgrowth). This macrosomia is associated with in increase insulin secretion and overstimulation of the insulin producing beta cells during fetal life, though later in life a reduced insulin secretion is found (Van Assche et al., 2001).

Animal studies have shown that adaptations are made by the fetus with regards to insulin production and use. Aerts, Holemans and Van Assche (1990) verified this when they destroyed pancreatic beta cells in maternal rats, thus making them diabetic, and found that their fetuses were then confronted with very high glucose levels being transported across the placenta. In response to this glucose overload, the fetus pancreas become larger and the beta cells more active. This hyperactivity of beta cells, which is associated with increased insulin release, is temporary and leads to disorganization and exhaustion of beta cells in the still developing pancreas, and thus hypoinsulinemia in the fetus (Van Assche et al., 2001).

There is a strong association between pregnancy in women with any form of diabetes and high infant mortality and morbidity in their offspring

(Stenninger, Flink, Eriksson & Sahlen, 1998). Over the past 25 years, the rate of neonatal mortality among infants of diabetic mothers has declined from 250 per 1000 live births to approximately 20 per 1000 live births. About half of these deaths are due to congenital malformations that result from the diabetic intra-uterine environment (Weintrob, Karp & Hod, 1996). The frequency of congenital malformation, as well as morbidity associated with maternal diabetes, is directly related to the severity of the diabetes (Ornoy et al., 1998). Abnormalities in systems such as the cardiovascular system, musculoskeletal, and central nervous system occur 5 times more often in the offspring of diabetic mothers. Rare abnormalities like sacral agenesis and caudal regression syndrome occur between 200 and 400 times more frequently than the non-diabetic population (Weintrob et al., 1996). Thus maternal diabetes and hyperglycemia may be responsible for an entire spectrum of embryofetopathy (figure 1), as explored by Carrapato (2003).

*Figure 1: Spectrum of embrofetopathy with maternal diabetes.**



** Carrapato, 2003*

Cohort studies, which follow the progress of infants born to diabetic mothers, have been undertaken to look at the effects of this sub-optimal intra-uterine environment. Population studies have indicated that there are lingering effects on the offspring of diabetic mothers. This has been complemented by studies of animals in which diabetes has been induced; offspring of such animals have abnormal metabolic consequences in adult life (Stenninger et al., 1998). Thus it has been proposed that diabetes in the mother has an effect on not only the fetus, by disrupting its environment, and the neonate in transition to a new environment, but also later on in life due to its programming effects on the organ systems of the body. Among the affected organs is the brain, the brain is particularly vulnerable during development, and alterations to its development may lead to long-term neuropsychological deficits. These deficits may be lessened by control of maternal diabetes, but this control may not be available to all populations. Thus more widespread diabetes treatment, especially in pregnant women, is needed to decrease the prevalence of fetal and long-term consequences of maternal diabetes.

Fetal Outcomes in Offspring of Diabetic Mothers

Macrosomia

The condition of macrosomia is defined as a birth weight far above that of the normal range, greater than 4000 g. This condition is associated with increased supply of glucose as well as overstimulation and secretion of insulin in fetal life. In humans, macrosomia is the most prevalent outcome in offspring of diabetic mothers. There are two forms of macrosomia: symmetric, a genetic form; and, asymmetric, a form that is induced by maternal diabetes. Asymmetric marcrosomia is characterized by beta cell hyperplasia with hyperinsulinemia, as well as a small head to abdominal and thoracic circumference ratio. The associated hyperinsulinemia induces increased glucose uptake and fat synthesis, this is partly due to increased insulin as a growth factor in late gestation (Van Assche et al., 2001; Weintrob et al., 1996). This increased fat synthesis is not equally distributed; it selectively affects the areas of the heart, liver, and subcutaneous fat. It has been shown that tight insulin control of pregnant diabetic mothers reduces the rate of macrosomia (Weintrob et al., 1996). Langan, Deary, Hepburn and Frier (1991), as well as others looking for methods to prevent macrosomia, have found that when blood glucose levels are maintained at levels between 4.8-5.8 mmol/L, the mean blood glucose level found in non diabetic pregnant women, the most optimal birth weight results. It was also found

that for every 1 mmol/L increase in glucose level, a 36.6 g increase in birth weight occurred (Weintrob et al., 1996; Yang et al., 2004). Thus it is the increased level of glucose in the fetal system that triggers macrosomia.

This disproportionate fetal growth is associated with increased fetal morbidity at the time of delivery, including an increased rate of cesarean deliveries (Setji et al., 2005). Other associated delivery complications include shoulder dystocia, where the shoulder becomes pressed against the mother's pubic bone and can result in permanent neurologic injuries, clavicle fractures, brachial plexus injuries, damage to the network of nerves within the neck and shoulder that are supplied by nerves exiting from the spine, as well as asphyxia, and oxygen deprivation (Weintrob et al., 1996). These occur as the result of the large size of the neonate in comparison to the birth canal. Thus it is common for cesarean delivery to be used, although this comes with its own consequences for both mother and infant (Carrapato, 2003).

Congenital Malformation

Although there has been a decrease in infant mortality in cases of maternal diabetes since the 1960s, there has been an increase in the frequency of diabetes-related congenital malformations. These malformations account for about 50% of all neonatal mortality. The frequency of congenital malformations in infants of diabetic mothers is about 2-4 times higher than in those born to non-diabetic mothers (Weintrob et al., 1996). In a study conducted by Casson et al. (1997), it was found that neonatal mortality was 4 times higher, and still birth was 5 times higher in insulin-dependent diabetic mothers, than in the general population (Table 1, next page). These numbers are proposed to be linked to fetal congenital malformations, as the prevalence of congenital malformations in this population was 10 times higher than the general English population (Casson et al., 1997).

Congenital malformations are permanent physical defects that may or may not be genetically influencd. They occur when the development of a structure is arrested, delayed, or misdirected in fetal life. Congenital malformations may involve any, or multiple, organs or organ systems including, but not limited to, the heart, lungs, liver, intestinal tract, bones, and brain (MedicineNet.com).

This high rate of malformations occurs because by 8 weeks gestation, most of the organs have formed into rudimentary ones. This happens before some women are aware they are pregnant, and before most have sought medical attention; thus adequate glycemic and insulin control may not be in place,

and may interfere with organogenesis (Weintrob et al., 1996). It is not known if malformations are the result of maternal hyperglycemia or if they may also result hypoglycemia (at least in the case of untreated gestational diabetes) since malformations in animal models have been shown to result from episodes of hypoglycemia (Ter Braak et al., 2002).

Table 1: Congenital malformations and mortality rates in study sample of England and Wales and Merseyside and Cheshire (1990-4)

	Study Population (95% CI)	England & Wales	Merseyside & Cheshire
Stillbirth rate/1000 total births	25.0 (8.9 to 41.4)	5.0	4.7
Perinatal mortality rate/1000 total births	36.1 (16.8 to 55.4)	8.3	7.6
Infant mortality rate /1000 live births	19.9 (5.3 to 34.6)	6.8	6.1
Prevalence of congenital malfomations/1000 live births	97.2 (66.6 to 127.8)	9.8*	NA
Prevalence of congenital malfomations among all liveborn infants /1000 live births	94.0 (63.5 to 124.5)	9.5*	NA
Prevalence of congenital malfomations among liveborn boys/1000 live births	101.8 (55.9 to 147.7)	10.8*	NA
Prevalence of congenital malfomations among liveborn girls/1000 live births	88.4 (47.0 to 129.8)	7.9*	NA

(Casson et al., 1997) (reprinted with permission).

Hypoxia

Fetal hyperinsulinemia, which is the result of excess glucose transport from the maternal system, results in increased metabolic rates, and thus oxygen consumption at the cellular level. This, along with altered oxygen transport, leads to a condition of fetal hypoxia, which has also been proposed to account for a proportion of stillbirths and asphyxia in infants of diabetic mothers (Carrapato, 2003). The effects of hypoxia and its effects on glucose oxidative metabolism in the brain has been explored in rats. These rats, along with their day 3 offspring, were placed in an oxygen low chamber (9.5% oxygen versus 21% oxygen that is present in air) that simulated a hypoxic environment. It was found that enzymes of glucose oxidative metabolism in the brain were significantly increased – by 100-370% for lactate dehydrogenase, and 15%-30% for hexokinase – when compared to rats and their dams in normoxic (21% oxygen) conditions. The major areas

of the brain that showed these enzymatic alterations were the cerebral cortex, olfactory bulb, hippocampus, hypothalamus, pons, medulla, cerebellum, and midbrain (Lai et al., 2003).

In fetuses of diabetic mothers, hypoxia is the result of an increased affinity of oxygen for glycosylated hemoglobin in the mother. (Hemoglobin is the molecule in red blood cells used to transport oxygen. Normally, this is not glycosylated; in people with diabetes, levels of glycosylated hemoglobin are elevated as the result of hyperglycemia.) The hyperglycemic environment also results in erythroblastosis in the fetus which is accompanied by a delay in the switch from embryonic to fetal hemoglobin chain production (Al-Mufti, Hambley, Farzaneh, & Nicolaides, 2004). During periods of hypoxia, the fetus is reliant on the activation of a growth-driving cascade, the hypoxia-inducible factor (HIF) cascade. The upregulation of HIF in hypoxic conditions leads to expression of genes encoding vascular endothelial growth factor, thus increasing vascularization, as well as erythropoietin, to increase red blood cell production for the transport of oxygen. It also results in increased expression of glucose transporters and glycolytic enzymes. Unfortunately in the hypoxia condition of fetuses of diabetic mothers, glucose is already present, in abundance. This hyperglycemia, which initially is enhanced by HIF, causes a negative feedback of the hypoxia-inducible factor cascade by degrading HIF (Lampl & Jeanty, 2004). Thus, the fetus is faced with a conundrum due to the overly abundant glucose availability and inevitable hypoxia. Consequences of hypoxia include increasing the level of glucose available for neurons, with glucose signalling its own sufficiency, thus prematurely turning the adaptive mechanisms off, and starving the body and brain of oxygen (Lampl & Jeanty, 2004). This oxygen deprivation is implicated in infant mortality, as well as in later pathology (Lai et al., 2003).

Short Term Neonatal Outcomes for Infants Born to Diabetic Mothers

Although the following neonatal complications may occur in the general neonatal population, the prevalence in the infants born to diabetic mothers is much higher. The frequency appears to be dependant upon the severity of the maternal diabetes and the degree of glycemic control during gestation. Also, the prevalence of neonatal adverse outcomes is higher in those infants born to mothers with type 1 diabetes than those with the gestational form (Weintrob et al., 1996).

Hypoglycemia

Hypoglycemia (low blood glucose levels) in neonates, can occur within a few hours after delivery. This short supply of blood glucose in the neonate is present in 10-25% of all infants born to diabetic mothers. The severity of the neonatal hypoglycemia is dependent upon the maternal glucose control in late gestation as well as during parturition (Weintrob et al., 1996). On the basis of studies in animal models, this is thought to be the result of the maternal hyperglycemic state which induces fetal hyperinsulinemia (Setji et al., 2005; Weintrob et al., 1996). Insulin is stored and released from the beta cells of the pancreas. However with the excessive stimulation that is caused by hyperglycemia in fetuses of diabetic mothers, pancreatic beta cells eventually lose their stores of insulin. Neonatal hypoglycemia should be tested for and treated without delay. This is accomplished by early feeding or providing intravenous glucose to the infant (Weintrob et al., 1996).

Hypocalcemia and Hypomagnesemia

Infants of insulin dependent diabetic mothers have a high rate of neonatal hypocalcemia and hypomagnesemia. Infants born to mothers with gestational diabetes also are at risk for these disorders. The etiology of these disorders is not well understood, but may be related to underfunction of the neonatal parathyroid glands and/or maternal magnesium deficiency resulting from the diabetes (Salle, Delvin, Glorieux & David, 1990).. Fortunately, these disorders often resolve within 48-72 hours without any significant consequence.

Polycythemia and Hyperbilirubineamia

The frequency of polycythemia, a stem cell and marrow disorder that results in an elevated and uncontrolled red blood cell production,, is 10-20% in infants of diabetic mothers (emedicine, 2006). This abnormal red blood cell production leads to a build up of bilirubin, a by-product of red blood cell breakdown, which is toxic in high levels. Those neonates displaying characteristics of polycythemia and hyperbilirubinemia are required to undergo phototherapy to aid their body's natural clearance of bilirubin. In extreme cases, blood transfusions are required (Weintrob et al., 1996).

Cardiomyopathy

Many of the infants born to diabetic mothers present with cardiac enlargement with septal hypertrophy. This cardiomyopathy appears to be secondary to the anabolic effects of fetal hyperinsulinemia (Weintrob et al.,

1996). This has been shown to be true experimentally in rats as well. Hypertension as well as bradycardia and abnormal vascular function overall have been shown (Holemans et al., 1999). This cardiomyopathy in humans, however, seems to resolve within 6 months of birth (Weintrob et al., 1996). In animal models, there is, nevertheless, a proposed effect in adult life of these offspring. It has been found that within the arteries of these offspring there are abnormalities, which may predispose them to later cardiovascular disorders. This may also occur through neuropathy as a result of maternal diabetes, which alters the sympathetic regulation of the synoatrial node (Holemans et al., 1999).

Respiratory Distress Syndrome

In the 1950s and 60s, the most common cause of neonatal death in infants born to diabetic mothers was respiratory distress syndrome (Weintrob et al., 1996). This increasing difficulty in breathing is caused by lung air sac collapse. Symptoms appear shortly after birth, and include unusual breathing, either rapid breaths or shortness of breath, brief stoppages of breathing, blue skin coloration, as well as limb swelling (Feng, 2006; Medline Plus Medical Encyclopedia, 2006). This may be the result of hypoglycemic stress in the fetus and neonate which results in the increased release of hormones, glucocorticoids, which have been implicated in lung maturation (Ter Braak et al., 2002). Increased production of glucocorticoid in the fetus results in precocious maturation of the lung, an abnormal state, and also may stimulate early parturition (Challis, Matthews, Gibb & Lye, 2000). Another factor contributing to neonatal respiratory distress syndrome in infants of diabetic mothers is the inhibitory influence of the fetal hyperinsulinemia state on the synthesis of surfactant, a lipid based substance produced by the lungs to aid in respiration by preventing the sticking together of air sac walls (Carrapato, 2003). To prevent the serious and fatal consequences of respiratory distress syndrome, lung maturity should be checked at delivery. Fortunately, with improvements in both diabetic control and pregnancy maintenance past 38 weeks gestation, rates of respiratory distress syndrome have decreased to that of infants born to non-diabetic mothers (Weintrob et al., 1996).

Long Term Outcomes for Offspring of Diabetic Mothers

Diabetes

Studies in different animal models indicate that the development of gestational diabetes results in an increased risk of diabetes in the offspring (Aerts & Van Assche, 2006). These laboratory data are supported by

epidemiological data from humans, which indicate that long range complications include an increased risk of impaired glucose tolerance or diabetes mellitus (Weintrob et al., 1996). Although there is evidence that pregestational and gestational diabetes have genetic predisposing factors, cumulative evidence suggests that intensive glucose control during pregnancy will result in a decrease in the frequency of these disorders in offspring.

Obesity

Obesity appears to be another long-term complication in those born to mothers with diabetes during pregnancy (Setji et al., 2005). In a cohort study performed in 1991 by Silverman et al. (1991), in which infants born to diabetic mothers were followed from birth up to 8 years of age, it was found that beginning at age 5 their body weight increased considerably. By the age of 8, half of these children were categorized within the 90th percentile for body weight for those not born to mothers with diabetes. They also proposed that fetal hyperinsulinemia is a good predictor of childhood obesity (Weintrob et al., 1996). Also, it is known that obesity is a risk factor for type 2 diabetes, in and of itself.

Neuropsychological Deficits

Abnormal glucose levels, both high and low, have been implicated as potential teratogenic agents for fetal organ development, this has been shown in animal models where maternal diabetes is induced, and organ pathology is observed after birth of the offspring. This altered glucose environment may have a long-term effect on the offspring, including neuropsychological deficits (Ter Braak et al., 2002). This is because the brain is an immense consumer of glucose. The human brain requires about 20% of the body's metabolic consumption for its normal functioning. If deprived of this, even temporarily, brain function is negatively affected (Deary & Frier, 1996). Since glucose is a requirement for brain function and development, it is transported across the blood-brain-barrier by a facilitative glucose transporter GLUT. Different isoforms, GLUT1, GLUT2, GLUT3, GLUT4, and GLUT5, of this transporter become expressed at different times of development. These transporters are composed of proteins. However glucose may act within cells to up or down regulate the expression of these proteins and thus its presence in the brain. These effects may be irreversible (Lampl & Jeanty, 2004).

Experimentally, the importance of glucose in brain development has been shown by Smoak and Sadler (1990) in mouse embryos. When glucose levels

were reduced by 50% for 2 hours in neurulating mice, which are in the stage of neural tube and neural crest cell creation, dysmorphogenesis resulted. Smoak and Sedler also found that those mice undergoing gastrulation were more sensitive to even shorter periods of hypoglycemia (Smoak & Sadler, 1990). In humans, differentiation and maturation of the brain cortex increase near the end of the second trimester; thus this is also a time of vulnerability for the brain, and any alteration to its environment may lead to an altered neurology (Carrapato, 2003; Ornoy et al., 1998). Akyol et al (2003) have proposed that hypoglycemia, which may be brought on by hyperinsulinemia in the offspring of diabetic mothers, may cause damage to the neurons of the medial temporal region of the brain. In one publication they noted, with the use of CT and MRI scans, global cerebral atrophy in one individual who had suffered repeated episodes of severe hypoglycemia, hyperglycemia and convulsive episodes. As well severe perfusion defects were found in brain regions associated with memory processing (Akyol et al., 2003). Such neurological effects of altered glucose levels may explain the findings that offspring of diabetic mothers tend to have poorer academic performance as well as other neuropsychological deficits. These deficits tend to be classified into four main areas - intelligence and memory, psychomotor, sensory, and attention and hyperactivity.

Intelligence and Memory

Offspring of diabetic mothers exhibit neuropsychological deficits, which include poorer intellectual performance and deficits in memory recognition. Langan et al. (1991) found that in adults with insulin-treated diabetes, instances of severe and recurrent episodes of hypoglycemia were associated with cumulative cognitive impairment, as assessed with the Wechsler-Revised I.Q. test, as well as memory and information-processing speed.I n 1997, Rizzo, Metzger, Dooley and Cho reported on their study of the offspring of 139 women with diabetes in pregnancy. These offspring were assessed with the Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Kaufman Test of Educational Achievement. Scores on the WISC-R, as well as on other tests of intellect, were inversely correlated with maternal glucose metabolism in the second and third trimesters of pregnancy. Thus they concluded that poorer child performance was associated with poorer maternal metabolic control during gestation (Rizzo et al., 1997).

The hypothesis that infants born to mothers with diabetes during pregnancy would be prone to hippocampal damage from altered glucose levels during fetal development, and thus recognition memory deficits, was derived from animal models of hypoglycemia, chronic hypoxia, as well as iron deficiency

in the fetal and immediate postnatal stages of life (Nelson et al., 2000). Recognition memory is essential for cognitive functioning. The evaluation of recognition memory in infants was assessed by Deregnier, Nelson, Thomas, Wewerka and Georgieff (2000) in hopes of determining the association between diabetes as a perinatal risk factor and memory. They used event-related potentials (ERP), which are a type of evoked potential present in electroencephalograms (EEG) used in the field of cognitive neuroscience in the exploration of neural pathways. It was found that in animal studies, the hippocampus in particular, an area required for recognition memory, was affected by hypogylcemia. Since this form of memory is correlated with intelligence, they also hypothesized that these ERPs would have a correlation with cognitive development as assessed at age 1 with the Bayley Scales of Infant Development. The infants in both groups, those of mothers with diabetes and those of mothers without diabetes, showed evidence of better recognition of their mother's voice than to that of a stranger. However, those infants born to mothers with diabetes during pregnancy had shorter latency measurements, which is a reflection of processing speed. Results on cognitive development through the administration of the Bayley Scale of Infant Development showed that there was a correlation between these scores and ERPs for both infants of diabetic mothers and controls. Thus they concluded that neonatal recognition memory, as measured by ERPs is correlated with infant cognitive functioning (Deregnier et al., 2000). This form of ERP evidence was also used by Nelson et al. (2000) in a study of 6-month-old infants of diabetic mothers. These authors found that the ERP measurements showed robust evidence consistent with memory deficits in these infants. Thus altered glucose levels can affect cognitive functioning, which may manifest itself as poorer memory and intellectual scores in offspring of diabetic mothers.

Psychomotor

Poorer psychomotor development, the attainment of skills that involve both mental and motor activities, has been implicated as a long-term neuropsychological deficit in offspring of diabetic mothers. This has been shown in adolescents of mothers with poorly controlled diabetes during gestation (Ter Braak et al., 2002). It has also been demonstrated that neonatal hypoglycemia is associated with minimal brain dysfunction in motor control at 8 years of age (Ter Braak et al., 2002). Thus altered glucose environments appear to be associated with psychomotor neuropsychological deficits after birth in infants born to mothers with diabetes (Lampl & Jeanty, 2004; Ter Braak et al., 2002).

Stenninger et al. (1998) performed a study on neonatal hypoglycemia and its relation to neurological dysfunction. They looked at 13 children with neonatal hypoglycemia and 15 without. Neural dysfunction in regions of the brain, for example the brainstem, was shown to occur at blood glucose levels below 2.6 mmol/L. In infants diagnosed with neonatal hypoglycemia, many have blood glucose levels below 1.5 mmol/L, thus dysfunction is likely. Of those children studied, eye-hand coordination and performance were often affected (Stenninger et al., 1998). It was also found that children born to diabetic mothers, when compared to normal controls, had impaired performance on indices of fine and gross motor functions (Ornoy et al., 1998). This also was shown by Rizzo et al. (1995) in children ages 6-9 in a cohort-analytic study. These children were assessed with the psychomotor indices of Bayley Scales of Infant Development and Bruininks-Oseretsky Test of Motor Proficiency. Their scores on the Bruininks-Oseretsky Test of Motor Proficiency were correlated with maternal metabolism in both the second and third trimesters of gestation. Both of these periods are associated with rapid and essential brain growth and development (Rizzo et al., 1995). Thus prenatal maternal metabolism abnormalities contribute to poor psychomotor development in their offspring.

Sensory

Even in cases where no gross neurological defects were found, Stenninger et al. (1998) found minimal brain dysfunctions in children with neonatal hypoglycemia who were born to diabetic mothers; in particular, their scores were significantly lower in areas of hearing and speech. The slow development of language and speech was also a common feature of these children (Stenninger et al., 1998). This was also found by Hannonen, Tupola, Ahonen & Riikonen. (2003) when they applied the NEPSY, a developmental neuropsychological assessment tool that is used to assess development in attention and executive functions, language, sensorimotor functions, visuo-spatial processing, as well as learning and memory, to children that had experienced severe hypoglycemia in the past as the result of having type 1 diabetes themselves. They found differences in these children, in comparison to children with diabetes who did not have a history of severe hypoglycemia as well as healthy control children, with regards to verbal short-term memory and phonological processing. Thus severe hypoglycemia may lead to deficits in auditory-verbal functioning and a barrier to learning for children.

Attention and Hyperactivity

The neurological damage present in children of mothers who were diabetic during pregnancy may not necessarily have an effect on their I.Q., but may cause deficits in their attention (Ornoy et al., 1998; Wenman, Joffres & Tataryn, 2004). Stenninger et al. (1998) found that those neonates who were afflicted with hypoglycemia at birth were more likely to be judged as easily distracted, overactive, and impulsive. This is in accordance with the minimal brain dysfunction screening test and physiological test they administered, where concentration and tendency to distraction have significant weighting (Stenninger et al., 1998). Also in 1998, Ornoy et al. tested the neurobehavioural functioning of children born to mothers with well-controlled diabetes during pregnancy and matched controls. They found that even when maternal diabetes was tightly regulated during pregnancy, the offspring scored higher on the Touwen and Prechtl neurological examination, which detects more prevalent soft neurological signs, and indicators of mild and non-specific brain damage. These children also scored poorer on the Pollack tapper test, which detects minor neurological deficits, inattention and hyperactivity. Both of these tests are used routinely as predictors of attention deficit and hyperactivity disorder (Ornoy et al., 1998). In accordance with these findings is a discovery by Stenninger et al. (1998) that children born with hypoglycemia had altered functioning in their fronto-parietal and fronto-temporal brain regions. This finding implicated overarousal, which is consistent with other studies of children with attention deficit and hyperactivity disorder (Stenninger et al., 1998). Therefore, the neurological deficits experienced by children born to mothers experiencing diabetes during pregnancy may not only effect their intellectual performance, but also may alter their levels of attention and hyperactivity as well, leading to a pathological state.

Diabetes during the time of gestation creates a sub-optimal environment for fetal development. This adverse environment has negative effects on organogenesis. One organ in particular, which is affected, is the developing brain. Any alteration to the precise formation of the brain and its circuitry has the potential to cause long-term neuropsychological deficits. In children born to diabetic mothers, impairments have been found in their intelligence and memory, psychomotor skills, sensory functioning, as well as their levels of attention and hyperactivity. Fortunately, with the enforcement of diabetes management as well as the availability of obstetrics and neonatal care, both the rate and severity of these neuropsychological deficits has declined significantly, however they may still exist, but in a subtle form (Weintrob et al., 1996). Thus it is important to identify those at risk for diabetes in

pregnancy, to tightly control their blood glucose levels, and prevent neuropsychological deficits in the following generation.

Treatments

In 1989, the St. Vincent declaration set the target of reduction in negative pregnancy outcomes among diabetic women to the level of non-diabetic women, in five years (Casson et al., 1997). The 'glucose hypothesis' assumes that it is the abnormal glycemic levels in the mother that lead to these fetal consequences (Sunday & Eyles, 2001). Thus control of blood glucose levels in the mother is proposed to decrease the adverse pregnancy outcomes in women experiencing diabetes during gestation. The most common way of controlling glycemic levels is through multiple daily injections of insulin (Ter Braak et al., 2002). However the treatment of diabetes has both positive aspects and negative aspects.

Worldwide, there is acknowledgement that the decline of neonatal mortality and morbidity in offspring of mothers with diabetes, specifically type 1 diabetes, is due to improved diabetic control of mothers, including self-blood-glucose monitoring and insulin therapy. Preconceptional control of diabetes, fetal monitoring and intensive neonatal care units have also played a part in this decline (Ter Braak et al., 2002; Casson et al., 1997; Weintrob et al., 1996). Two regimes have been compared for metabolic control during pregnancy, multiple daily injection treatment and continuous subcutaneous insulin infusion, both giving promising results in randomized clinical trials (Ter Braak et al., 2002). With better maternal control of diabetes, the outcomes for offspring appeared to improve. Improvements included a decrease in neuropsychological deficits and the appearance of normal I.Q. scores (Stenninger et al., 1998).

Although the tight control of maternal type 1 diabetes has made significant impact on fetal health, it is not easy to achieve. As well, it comes with maternal consequences due to the unique nature of pregnancy as an insulin resistant state. In the mother with type 1 diabetes, strict glycemic control is often associated with an increased incidence of potentially life-threatening hypoglycemia. There also is a high prevalence of rebound hyperglycemia even with treatment, which could explain the still high rates of both malformations and macrosomia. Thus to prevent this rebound effect, treatments should avoid blood glucose levels below 3.9 mmol/L, the hypoglycemia range, to prevent the cycle of adverse glucose counterregulation that occurs with insulin treatments (Ter Braak et al., 2002). Another drawback of modern treatments is the lack of knowledge

about effectiveness of different treatments for the different forms of maternal diabetes and the fetal consequences of such treatments. Although it has been shown that well controlled diabetes is associated with fewer fetal consequences, this occurs in a selective population of those with access to specialized centres and health care (Casson et al., 1997). Therefore in the general population, the tight control of diabetes has not really made as significant an impact as first thought.

Future Aims for Improvement of Outcomes for Offspring of Diabetic Mothers

In the Western world, the tight control of diabetes during pregnancy has become procedure. However, ideally this control should start from the beginning of pregnancy, not at the time of diagnosis in pregnancy (Ter Braak et al., 2002). A rapidly acting insulin analogue called lispro has been approved of recently for glycemic control. Available data suggest that it is useful during pregancy in women with preexisting diabetes (Lapolla, Dalfra & Fedele, 2005). Other derivatives are under evaluation.

One major aim for future improvement in the outcomes of offspring of mothers with diabetes is greater awareness of these consequences related to maternal diabetes and what can be done to prevent them. It was found that only 30-60% of women who had diabetes before pregnancy were referred to special clinics before conception (Weintrob et al., 1996). This is not adequate since damage and programming can occur in the fetus before the mother is even aware she is pregnant. Thus women with diabetes should be educated about the impact of their illness on pregnancy before the decision to get pregnant is made. Education and knowledge about the effects of diabetes in pregnancy should be made apart of public education and awareness, like the consequences other teratogens have.

Our First Nations People: Case Study of a Population at Risk for Diabetes, and the Complications Associated With it

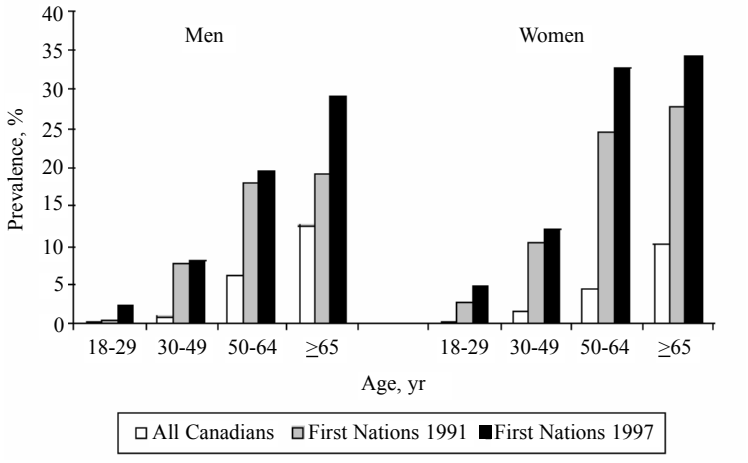
Incidence: Diabetes, A New Epidemic

In the First Nations population of North America, before the 1940s, diabetes was a highly uncommon disease. It was so rare that most aboriginal languages had no word to describe this disease (Hernandez, Antone & Cornelius, 1999). Unfortunately, in today's world, diabetes has reached an

"epidemic" magnitude among the First Nations people. The majority of this population is afflicted with type 2 (insulin independent) diabetes, and they tend to develop this form of diabetes earlier in life than Caucasian Canadians (Hernandez et al., 1999). The prevalence for type 2 diabetes in the non-aboriginal population varies between 2-5%; however in certain First Nations populations the prevalence is as high as 15% (Sunday & Eyles, 2001). A Statistics Canada census undertaken in 1991, which surveyed all self-identified First Nations, Inuit and Metis, as well as the First Nations and Inuit Regional Health Survey of 1997, found a prevalence of approximately 8% for men and 13% for women (Figure 2, next page). This is a prevalence 3.6-5.3 times higher than the general Canadian population, when age adjustments are made (Young et al., 2000). This increased prevalence among Aboriginal populations in Canada only became evident in the past 20 years, thus was a rapid increase. For example in Saskatchewan, the rate doubled in one decade, where as in Sioux Lookout Zone of northwest Ontario, it increased 45% (Sunday & Eyles, 2001; Young, Reading, Elias & O'Neil, 2000). The prevalence and outcomes of diabetes in the population of our First Nations People is determined by various methodologies, mainly statistics derived from census surveys, health surveys, death certificates, registries of diagnosed cases as well as screening surveys (Sunday & Eyles, 2001; Young et al., 2000).

Both those health care personnel working in the community and those of the community are aware that diabetes is one of the principal heath care concerns in the First Nations People of Canada (Canadian Diabetes Association. Aboriginal Section, n.d.). The onset of diabetes, mainly type 2, is thought to be the cause of both genetic and environmental factors (Sunday & Eyles, 2001). The most accepted explanation for this rise in prevalence is however, that it is a combination of these two factors. Since world war two, the lifestyles of many First Nations people have changed; this may be connected to an existing genetic susceptibility for type 2 diabetes (Sunday & Eyles, 2001;Young et al., 2000). Obesity, a risk factor of type 2 insulin independent diabetes, has also increased in prevalence among Canadian First Nations populations. The Sandy Lake Study found a correlation between leptin, a hormone produce by fat tissue, and plasma insulin, suggesting that obesity is a cause of high insulin levels. This increased body weight in Aboriginal populations is associated with a move away from traditional foods towards modern foods, as well as a decrease in physical activity. The embracing of a lifestyle that is less active in nature is seen as a natural phenomena that accompanies a transition to a modern, Western diet, and is seen in most populations adapting to a Western culture (Young et al., 2000).

Figure 2. The prevalence of self-reported diabetes among all Canadians (1994) and First Nations people (1991 and 1997). (Young et al., 2000).



Another theory that may hold some validity is known as the "thrifty genotype" theory. This theory proposed that Aboriginal populations are more prone to diabetes due to evolutionary adaptations. In the times of hunting and gathering societies, this adaptation allowed for a prompt insulin production response to any rise in blood glucose levels. This aided in the storage of glucose as triglycerides in fat cells, to be used in times of food shortages. However, due to the ample access to food in today's society, this rapid insulin increase, prompted by slight increases in blood glucose, results in hyperinsulinemia and insulin resistance by cells (Young et al., 2000).

The Sandy Lake Study, which allowed for systematic genomewide screening, has given rise to a lot of genetic data. It revealed 4 markers which are associated with diabetes. One of which is a new variant of a gene, thought to be unique to the Oji-Cree population, that encodes for the hepatic nuclear factor-1α. This allele is two times more prevalent in those with diabetes than those without, and those homozygous for it (i.e., have inherited two copies of this allele) tend to develop type 2 diabetes at an earlier age (Young et al., 2000).

The importance of this high prevalence in diabetes in the First Nations population is appreciated when long-term health consequences are taken into consideration. In the adult, type 2 diabetes increases the risk for

cardiovascular disease, dysfunction in the kidneys, eyes, and nervous system, as well as compromised quality of life. Those Aboriginals with diabetes have been shown to have higher rates of hospitalization, readmission as well as longer stays once admitted (Young et al., 2000). The consequences of diabetes also extend to First Nations women, who are pregnant or plan to become pregnant, and their offspring.

Although in the general population the introduction and enforcement of insulin as a diabetic control measure has lead to a decrease in pregnancy loss and complications, within certain populations, First Nations included, the rate of gestational consequences remains high (Casson et al., 1997). Wenman et al. (2004) found that Aboriginal women were more likely to have diabetes, and had poorer outcomes when compared to other Canadian women, in their collection of data from obstetric practices, patient questionnaires, as well as microbiological data collected from the women studied. One such outcome was an increased prevalence among Aboriginal women to give birth to infants with macrosomia. Overall, First Nations women had infants with higher mean birth weights when compared to other Canadian women (Wenman et al., 2004). Gestational diabetes is one factor which contributes to high birth weight, and it is seen in 13% of pregnancies in First Nations women, compared to 4% for the general population. This also predisposes the next generation to type 2 diabetes, thus validating the 'genetic susceptibility in an unhealthy environment' theory of the epidemic increase of diabetes in the First Nations population (Young et al., 2000).

Barriers to Treatment

In today's world, interventions for diseases no longer depend solely on the presence of the pathology, but on the prospective of risk for developing it. As indicated above, one population considered at higher risk for the development of diabetes and the complications associated with this disease in Canada is our First Nations people. The perception of this risk however is not just medically defined. It has links to cultural values and beliefs; thus according to Sunday and Eyles (2001) it is a construct that occurs within social and political relations. Thus, due to the variance in values and beliefs in the Canadian population, traditional Western models for the care and treatment of diabetes have been unsuccessful in some segments of the population, including our First Nations people. Although many of our First Nations people reside in areas that are geographically remote, and thus have limited access to certain services, this logistical problem is not the sole barrier to treatment of diabetes in this population (Young et al., 2000; Hernandez et al., 1999).

It is generally known that the Aboriginal population is more prone to diabetes, however due to social and cultural factors, diagnostic testing in the population is lower than in the general population. The majority of First Nations peoples do not regularly visit a medically trained professional, for example, for a yearly physical. Among those who have been diagnosed with diabetes, this diagnosis was the result of the patient seeking attention for another ailment, not including the traditional signs of diabetes (Sunday & Eyles, 2001). Although diabetes is rampant in this population, these patients are often astonished by this news. This is due to the fact that since diabetes is a new phenomenon in their community, it has not yet been assimilated into the social framework. Thus for those diagnosed with diabetes in the First Nations population, this news is an isolating factor and makes them feel distant from their community. Many feel emotionally depressed at the thought of living with a chronic disease and may deny or ignore the fact that they have one. This is an important barrier to seeking treatment. Omitting the social and emotional consequences of diabetes, an important portion of the Aboriginal conception of health, and focusing on just the physical aspect of the disease may create a barrier for our First Nations people in seeking treatment (Sunday & Eyles, 2001). Thus it is important for health care professionals to understand this 'holistic' health concept to understand the way Aboriginal people see diabetes and how to best help them cope (Young et al., 2000; Sunday & Eyles, 2001).

Another barrier to the treatment of diabetes in our First Nations people has to do with understanding the causes they see as responsible for their disease, and the implications this may have on their tentativeness about mainstream treatments. Hernandez et al. (1999) discussed in her 1999 paper on the experience of diabetes of the insulin independent form in First Nations people two general explanations for diabetes, as proposed by Garro (1995). Firstly, some may blame themselves for their illness, attributing cause to unhealthy eating and lifestyle. The trend towards modern food versus traditional foods is a widely believed, and a valid, cause to this drastic increased prevalence of type 2 diabetes in First Nations populations (Hernandez et al., 1999; Wenman et al., 2004; Young et al., 2000). The second explanations for diabetes used by our First Nations people in understanding their own diabetes is that of blame towards the White man. This blame includes the White man's proposed corruption of Aboriginal society as well as pollution of the environment. This leads to not only a mistrust of health care professionals, but also of "White man's medicine", thus creating a huge barrier for treatment (Hernandez et al., 1999; Young et al., 2000).

Possible Solutions for Treatment for Diabetes in the First Nations Population

In Canada, there has been a political push for the recognition of diabetes as a major health concern for Aboriginal people. This is both at the local and federal levels. The Assembly of First Nations has worked at the national level to increase the awareness and research into diabetes in First Nations peoples, as well as developing prevention strategies. In 1995, Canada played host to the *Third International Native Diabetes Conference*, further raising the awareness of this health problem (Sunday & Eyles, 2001). In the 1999 federal budget, the *Canadian Diabetes Strategy* announced a five year, $115 million strategy to deal with diabetes in Canada, $58 million has been allocated to the *Aboriginal Diabetes Initiative* (ADI), a partnership between the Aboriginal people and Health Canada (Heath Canada, n.d.).

The treatment and primary prevention of diabetes both involve education. According to Sunday and Eyles (2001), the knowledge of a disease is the means of protection from the potential threat of it. Primary prevention of diabetes in this population involves educating about the protective effects of healthy behaviours. In First Nations populations in particular, it is important to combine this with a supportive environment because of the strong community aspect of their culture, respecting and incorporating traditions, and learning styles. This method of community education and support has been implemented in a few areas across Canada, focusing on schools and community gatherings (Young et al., 2000). One other way to break down barriers to treatments is adopting a teaching style more in tune with the First Nations culture. Traditionally Aboriginals have taught by example and sharing of experiences, thus this is proposed to be a solution. Having people from the community with diabetes showing others how to cope, as well as promoting preventative measures is one way to increase the effectiveness of the dissemination of diabetes information in these communities (Hernandez et al., 1999). To stop the epidemic of type 2 diabetes in the First Nations population, barriers to prevention and treatment must be broken. This can only be done with understanding and adaptation to the uniqueness of this population.

Conclusions

Due to the requirement of shared maternal nutrients, pregnancy is a natural diabetic state. This occurs because the placenta releases hormones that cause insulin resistance in the maternal system, thus a state of hyperglycemia. Maternal hyperglycemia is fetal glycemia. However, since the fetus is in a state of development, it is vulnerable to environmental changes. Barker et al.

(1993) hypothesized that any alteration to the fetal environment that has a potential effect on its growth and development will have long-term consequences. Maternal diabetes, with its altered glucose levels, represents an altered fetal environment since excess glucose is shunted into the fetal system causing the fetus to make adaptations that may have consequences on organ development.

In the literature, the fetal, neonatal, and postnatal consequences for the offspring of diabetic mothers have been explored. This review summarized the effects of maternal diabetes on her offspring, with a focus on the long-term effects in brain function that results from brain development in a glucose altered environment. Neuropsychological deficits, which are associated with maternal diabetes, have been found in intelligence and memory, psychomotor development, sensory, and attention and hyperactivity.

However, it has been found that with tightly controlled blood glucose levels, these outcomes can potentially be minimized. Unfortunately, the treatment regimes used today are not ideal for all forms of diabetes. The development of type 2 diabetes specific treatments, as well as those safe for use during pregnancy, have yet to come. Also, some segments of the population still do not possess adequate control of their diabetic condition, and thus are still exposed to its consequences. Our First Nations people are one such population. As a community, they have experienced epidemic like increases in type 2 diabetes in the past 20 years. Due to barriers in treatment, they are still at risk for the more severe consequences of uncontrolled diabetes, including those consequences for infants born to diabetic mothers.

Diabetes, no matter what the form, can and should be controlled to the best of the individual's ability. Although type 1 occurs in childhood and cannot be prevented, following the dietary and therapeutic regime prescribed by the doctor is the best way to prevent further complications that result from this disorder. In many cases, type 2 diabetes may be prevented, or its effects minimized, by eating healthy and living an active lifestyle. However, maintenance of optimal blood glucose levels is imperative, whether it be through dietary control, or insulin control, as prescribed by a physician to control diabetes. This should be done at all times, but particularly when contemplating conception, and during pregnancy. In this way an intra-uterine environment closer to the optimal may be reached, thus minimizing the risk of permanent programming effects on fetal organ growth and development. One step towards this ideal is through education of mothers, and mothers to be, on how to maintain a healthy life style, no matter their diabetic status (diabetic, non-diabetic, at risk diabetic), thus increasing the chance of healthy offspring.

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Glossary

Adipocytes. Fat storing cells.

Asphyxia. Lack of oxygen supply to tissues in the body.

Bayley Scales of Infant Development. A psychological test which id used to measure the developmental progress of infants and consists of three scales: mental, motor, and behaviour.

Beta cells. Cells in the pancreas that produce insulin.

Bilirubin. A breakdown product of heme of hemoglobin.

Brachial plexus injuries. Damage to the network of nerves within the neck and shoulder that are supplied by nerves exiting from the spine.

Bradycardia. Slow heart rate, usually defined as less than 60 beats per minute.

Bruininks-Oseretsky Test of Motor Proficiency. A measure of gross and fine motor skills.

Cardiomyopathy. Disease in which the myocardium, heart muscle, is effected. Are three forms I) Dilated, in which heart muscles become weak and enlargement (dilatation) of the heart chambers occurs, ii) Hypertrophic, where the heart muscle itself is much thicker than normal, and iii) Restrictive, in which the heart becomes stiff and cannot fill efficiently.

Caudal regression syndrome. A rare congenital defect, characterized by the absence of the sacrum, and defects of variable portions of lumbar spine, associated with anomalies of different systems.

Congenital malformation. Physical defect in any organ or organ system in which the development of the structure is arrested, delayed, or misdirected early in embryonic life and the effect is permanent, it may be caused by a genetic factor or by prenatal events.

Diabetes. A disease in which the body does not produce or properly use insulin.

Diabetogenic. Causing a state of diabetes.

Dysmorphogenesis. Anatomical malformation during development.

Electroencephalograms. A neurophysiologic technique which measures ongoing brain electrical activity generated by the neurons.

Embrofetopathy. Disease, especially its structural and its functional effects, in the embryo/fetual stages of life.

Eosinophils. A type of white blood cell containing eosin-staining granules. Which is known to destroy parasitic organisms and play a major role in allergic reactions, as well as secretion of chemical mediators that can cause bronchoconstriction in asthma.

Erythroblastosis. Destruction of red blood cells.

Erythropoietin. A hormone produced by specialized kidney cells that regulates red blood cell production in the marrow.

Etiology. The study or theory of the origins and factors which are the cause of a disease and the how it is introduced into the host.

Event-related potentials. A type of evoked potential present in electroencephalograms which are used in the field of cognitive neuroscience in the exploration of neural pathways.

Hexokinase. First enzyme of glycolysis, which converts intracellular glucose to Glucose-6-Phosphate.

Hyperbilirubinemia. A level of biliruin in the blood that is too high and potenitally toxic.

Hyperinsulinemia. A level of insulin in the blood that is too high.

Hyperplasia. An increase in, or the excessive growth of, normal elements.

Hypertrophy. An increase in cell size without an increase in cell number.

Hypocalcemia. A level of blood calcium that is too low (less than 7mg%).

Hypoglycemia. A blood glucose level which is too low to provide enough energy for body functions.

Hypomagnesemia. A level of magnesium in the blood that is too low.

Hypoparathroidism. Not enough parathyroid hormone resulting in abnormally low levels of calcium in the blood.

Hypoxia. A state of oxygen deficiency in the body, caused by the reduction in partial pressure of oxygen, inadequate oxygen transport, or the inability of the tissues to use oxygen, which is sufficient to cause an impairment of function.

Gastrulation. The process of movements and infoldings of embryonic cells destined to become endoderm in early animal embryos.

Genome. Entire complement of genetic material in a chromosome set.

Gestation. The period from conception to birth when a woman carries a developing fetus in the uterus.

Gestational diabetes. A transient diabetic state which occurs during pregnancy.

Glycolysis. A metabolic pathway that converts glucose to pyruvate (aerobic) or lactic acid (anaerobic).

Glycosylated hemoglobin. Hemogloibin with glucose attached to it.

Growth factors. Proteins that affect cell growth and division or an organism through its effects on cell differentiation and growth.

Hyperglycemia. An abnormally high level of sugar (usually glucose) in the blood.

Hypoglycemia. An abnormally low level of sugar in the blood.

Insulin. A hormone that is needed to convert glucose into energy within the cell.

Insulin resistance. A condition in which cells of the body are not able to utilize insulin to help glucose enter cells.

Islets of Langerhans. A cluster of endocrine tissue within the pancreas.

Kaufman Test of Educational Achievement. Designed to measure school achievement of children in areas of reading, mathematics, and spelling.

Lactate dehydrogenase. An enzyme (oxidoreductase) which catalyzes the conversion of lactate to pyruvate.

Macrosomia. A birth weight far above that of the normal range, greater than 4000 g.

Neuropathy. Disorders of neuronal function, especially of peripheral nerves, those that branch out of the spinal cord to all parts of the body.

Neuropsychological deficits. Impairment in the nervous system, especially the brain, and cerebral which lead to a declined mental functioning in areas such as language, memory, and perception.

Neurulation. Organogenesis of the nervous system in vertebrate embryos during which dorsal neuroectoderm cells of the neural plate (typically) roll up to form the neural tube which gives rise to central the nervous system.

Oral glucose tolerance test. This measures the body's ability to use a type of sugar, called glucose, that is the body's main source of energy.

Organogenesis. The part of embryonic development where the body's main organs are formed and developed.

Pollack tapper test. A neuropsychological test designed to detect minor neurological deficits, inattention, and hyperactivity.

Polycythemia. A stem cell and marrow disorder that results in an elevated and uncontrolled red blood cell production.

Proliferation. The continuous development of cells in tissue formation and reproduction.

Psychomotor development. The development of motor skills and movements which are produced by mental will.

Sacral agenesis. A term that applies to a wide range of developmental disorders of the lower portions of the spinal column and pelvis. In these disorders, some portion of the lumbar spine, sacrum, or pelvis is incompletely or incorrectly formed at the time of birth. Persons with such disorders often lack any useful motor functioning below the last normally formed level of the spine.

Shoulder dystocia. Shoulder becomes pressed against the mother's pubic bone and can result in can permanent neurologic injuries.

Streptozotocin-diabetic rats. Rats injected with an antibiotic, produced by an actinomycete (Streptomyces achromogenes) and active against tumors but damaging to insulin-producing cells, thus causing diabetes. Actinomycetes are a broad group of bacteria that produce thread-like filaments in the soil. They are responsible for the distinctive scent of freshly exposed, moist soil.

Surfactant. A lipid based chemical that decreases the surface tension of water, produced in the lungs.

Sympatheitic branch. Divison of the autonomic nervous system that is responsible for the fight-or-flight response.

Synoatrial node. A specialized bundle of neurons located in the upper part of the right atrium of the heart. It acts as the heart's natural pacemaker by firing at regular intervals causing a rhythmn.

Teratogen. An agent or influence that causes physical defects in the developing embryo.

Touwen and Prechtl neurological examination. A neurological examination for minor nervous dysfunction, or soft neurological signs; is a good predictor of attention deficits and hyperactivity disorder.

Type 1 (insulin dependent) diabetes. A state of diabetes characterized by the failure to produce insulin.

Type 2 (insulin independent) diabetes. A state of diabetes characterized by the inability to use insulin properly; may be combined with a decrease in insulin production.

Vascularization. The process whereby body tissue becomes vascular and develop blood vessels and capillaries.

Wechsler Intelligence Scale for Children-Revised. A general test of intelligence, composed of verbal and performance sections. In each subtest of the verbal scale, performance is in varying degrees dependent on specific knowledge, vocabulary, expressive language and memory skills. In the Performance scale, visual-spatial abilities, fine motor coordination, perceptual skills, and in some subtests speed, are essential for scoring.

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