NEONATAL MORBIDITY AMONG MACROSOMIC INFANTS IN THE JAMES BAY CREE POPULATION OF NORTHERN QUEBEC

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ABSTRACT

Gestational diabetes mellitus (GDM) and infant macrosomia are important obstetric health concerns for Native populations in Canada. Previous research in non-Native populations has established that GDM and macrosomia are associated with increased risk of fetal morbidity. Specifically, GDM is a risk factor for infant macrosomia, hypoglycemia, polycythemia, hypocalcemia, and hyperbilirubinemia. Furthermore, macrosomia is an independent risk factor for shoulder dystocia, clavicular fracture, brachial plexus injury, birth asphyxia and operative delivery. The main objectives of this study were to determine prevalence rates of GDM and macrosomia related neonatal complications for the James Bay Cree population of northern Quebec, and to identify risk factors for specific birth trauma injuries and metabolic complications in the population. The prevalence of macrosomia (≥ 4500 g) was 10.4%, and the estimated prevalence of GDM was 16.6% (95% CI 14.6-18.6) (n=229/1379). Shoulder dystocia was the most common birth trauma event among the Cree, affecting 2.5% (n=42/1650) of all Cree births, and 9.3% (n=16/172) of macrosomic deliveries ≥ 4500 g. The prevalence of neonatal hypoglycemia was also high, affecting 8.8% (n=144/1650) of all Cree newborns, and 18.1% (n=34/192) of GDM deliveries. Macrosomia (BW ≥ 4500 g) was a significant risk factor for shoulder dystocia, clavicular fracture, hypoglycemia, and caesarean section delivery. After adjusting for maternal age, parity, and gestational age, GDM was identified as a significant risk factor for macrosomia (≥ 4500 g), hypoglycemia, polycythemia, and hypocalcemia. In summary, this study identified a high incidence of neonatal complications among the James Bay Cree compared with rates in the general North American population. These outcomes can be explained, in part, by high prevalence rates of gestational diabetes and infant macrosomia. Further studies to investigate the long-term consequences of GDM and macrosomia related neonatal complications in the James Bay Cree population are warranted.

RÉSUMÉ

Le diabète gestationnel (DG) et la macrosomie fœtale sont deux complications obstétriques importantes chez les populations autochtones du Canada. La recherche chez les populations non-autochtones a déjà établi que le DG et la macrosomie fœtale sont reliés au risque élevé de morbidité pour le nouveau-né. Spécifiquement, le DG est un facteur de risque pour la macrosomie, l'hypoglycémie, la polycythémie, l'hypocalcémie, et l'hyperbilirubinémie. De plus, la macrosomie est un facteur de risque indépendant pour la dystocie de l'épaule, les fractures de la clavicule, les lésions du plexus brachial, l'asphyxie du nouveau-né, et les accouchements par césarienne. Les buts principaux de cette recherche étaient de déterminer le taux de prévalence des complications néonatales associées au DG et à la macrosomie chez les Cris de la Baie James, ainsi que d'identifier les facteurs de risque spécifiques étant liés à ces complications au sein de la population crie. La prévalence de la macrosomie (poids à la naissance ≥ 4500 g) était de 10.4%, et la prévalence du DG était de 16.6% (95% CI 14.6-18.6) (229/1379). La dystocie de l'épaule était la complication néonatale la plus commune chez les enfants cris, étant présente dans 2.5% (n=42/1650) des accouchements cris, et dans 9.3% (n=16/172) des accouchements macrosomiques ≥ 4500 g. La prévalence d'hypoglycémie néonatale était également élevée, affectant 8.8% (n=144/1650) des nouveau-nés cris, et 18.1% (n=34/192) des accouchements avec DG. La macrosomie (≥ 4500 g) était un facteur de risque significatif pour la dystocie de l'épaule, la fracture de la clavicule, et l'accouchement par césarienne. Le DG a été identifié comme un facteur de risque significatif pour la macrosomie (≥ 4500 g) après avoir ajusté pour l'âge de la mère, la parité, et l'âge gestationnel du bébé. En somme, cette étude était la première à identifier la prévalence élevée de complications néonatales chez la population crie de la Baie James. Ces complications peuvent être partiellement expliquées par les taux élevés de DG et de macrosomie fœtale au sein de cette population. Des recherches supplémentaires étudiant les conséquences à long terme causées par le DG et la macrosomie sont importantes.

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GLOSSARY

TERM	ACCRONYM
Brachial plexus injury	BPI
Cree Board of Health and Social Services of James Bay	CBHSSJB
Confidence interval	CI
Gestational diabetes mellitus	GDM
Impaired glucose tolerance	IGT
Last menstrual period	LMP
Low birth weight	LBW
National Diabetes Data Group	NDDG
Odds ratio	OR
Oral glucose challenge test	OGCT
Oral glucose tolerance test	OGTT
Relative risk	RR
Respiratory distress syndrome	RDS

INTRODUCTION

Over the past decade, several epidemiological studies have reported elevated prevalence rates of gestational diabetes mellitus (GDM) and infant macrosomia in Native populations across Canada (Thompson 1990, Dyck and Tan 1995, Harris et al. 1997, Caulfield et al. 1999, Rodrigues et al. 1999). These prevalence rates are an issue of concern given that GDM and macrosomia are each known to confer increased risk of maternal and fetal morbidity. Specifically, GDM carries an increased risk for infant macrosomia, hypoglycemia, polycythemia, hyperbilirubinemia, hypocalcemia, and hypomagnesemia, and for maternal pre-eclampsia and subsequent maternal type 2 diabetes (Person and Hanson 1998). Macrosomia, on the other hand, carries an increased risk for shoulder dystocia, clavicular fracture, brachial plexus injury (BPI), Erb's Palsy, birth asphyxia and operative deliveries (Bérard et al. 1998, Schwartz and Teramo 1999). In the longer-term, there is also evidence that macrosomic offspring of GDM pregnancies are at increased risk, compared with non-macrosomic offspring, of developing adolescent or adult onset type 2 diabetes and/or obesity (Van Assche et al. 1991, Silverman et al. 1995, Lindsay et al. 2000). Although these aforementioned GDM and macrosomia related neonatal and long-term complications have been studied in various non-Native populations, there is a paucity of such research among Native North American populations, where prevalence rates of GDM, macrosomia, and maternal obesity are particularly high.

In many Native Canadian communities, maternal prenatal nutrition recommendations and pregnancy weight gain guidelines have conventionally been geared towards reducing the incidence of LBW in order to improve neonatal/perinatal health outcomes. However, prevalence rates of LBW in many Native populations (2.8-5%) are on par with, or lower than, rates reported for the general Canadian population (5.0-5.5%), whereas prevalence rates of macrosomia (≥ 4500 g) are 3-4 times higher in Native versus non-Native populations (Thompson 1990, Dyck and Tan 1995, Armstrong et al. 1997, Luginaah et al. 1999, Caulfield et al. 1999, Rodrigues et al. 2000). Moreover, rates of GDM, an independent predictor of macrosomia, are similarly 2-3 times higher in Native versus

non-Native populations (Dyck and Tan 1995, Rodrigues et al. 1999a). In light of these observations, and our understanding that macrosomia and GDM are potentially preventable causes of infant morbidity and mortality (to be discussed in a subsequent section), it is important for health care practitioners in Native communities to be aware of the neonatal and long-term complications associated with these conditions.

Several theories have been proposed in the literature to rationalize the high incidence of macrosomia in Native populations. It is possible that evolutionary/genetic factors simply predispose Native women to deliver higher birth weight infants, either with or without increased neonatal morbidity and mortality. On the other hand, it is also possible that non-genetic factors (e.g., changes in diet, physical activity patterns, and lifestyle) are contributing to increased rates of GDM and obesity among Native women which are in turn leading to increased rates of macrosomia and infant morbidity. In support of this second theory, some researchers have noted a trend of increasing birth weight in North American Native populations since the 1960's that parallels the rising incidence rates of GDM and obesity among Native women (Dyck et al. 1995). Other researchers have not reported this same demographic trend for other Native populations (Armstrong et al. 1998). Regardless of whether or not the high birth weights observed in Native populations are caused by genetic factors, lifestyle factors, or a combination of both, it is useful to discern whether or not macrosomia is truly a significant neonatal health problem for Native populations, and to identify population specific birth weight cut-offs (e.g., $\geq$ 4000g, $\geq$ 4500, or $\geq$ 5000 g) that correspond with increased neonatal/maternal morbidity such as shoulder dystocia, Erb's palsy, and caesarean section delivery.

The following study was designed, in consultation with the Cree Board of Health and Social Services of James Bay (CBHSSJB), to record and report the prevalence of neonatal complications associated with GDM pregnancies and macrosomic deliveries for the James Bay Cree population of northern Quebec. The motivation for this project stems from findings of a previous study that identified exceptionally high prevalence rates of GDM (12.8%) and infant macrosomia (14.2% birth weight $\geq$ 4500 g) in the Cree population (Rodrigues et al. 1999a). The following thesis will present an up to date

review of the scientific literature pertaining to the definitions and predictors of, as well as the short and long-term complications associated with, GDM and macrosomia. Emphasis will be placed on explaining the predictors of and complications associated with GDM and macrosomia as they relate specifically to the health of Native people in Canada. In addition, this thesis will report statistical analyses and a discussion of the research findings drawn from maternal and neonatal information for the Cree population collected at health clinics and hospitals in the James Bay region (1994-1999). We hope that the conclusions derived from this study will serve the CBHSSJB and its team of health care practitioners to make informed decisions regarding their obstetric and neonatal care guidelines for GDM pregnancies and macrosomic deliveries in their population.

LITERATURE REVIEW - PART 1

GESTATIONAL DIABETES MELLITUS

Introduction

As previously mentioned, diabetes during pregnancy poses numerous short and long-term health problems for both mother and fetus. The most common neonatal morbidity associated with GDM is infant macrosomia, although hypoglycemia, polycythemia, hyperbilirubinemia, respiratory distress syndrome, and hypocalcemia have also been reported in the literature as significant outcomes of GDM pregnancies. There is also accumulating research evidence to support a metabolic relationship between increasing maternal glycemia and risk of neonatal morbidity (Sermer et al. 1995, Metzger et al. 1998). In light of this evidence, many practitioners advocate that macrosomia and other neonatal complications associated with GDM pregnancies can be prevented through encouraging GDM mothers to maintain tight control of their blood glucose levels either through diet or diet/insulin therapy. In order to understand the physiological associations between maternal hyperglycemia and neonatal morbidity, and the potential benefits of intensive GDM management to reduce the incidence of maternal and fetal morbidity, the following section will explore the pathophysiology, predictors of, and maternal and neonatal complications associated with GDM. Prevention of GDM and macrosomia related infant morbidities will be described in detail in part 2 of the literature review.

Pathophysiology of GDM

GDM is defined as glucose intolerance of variable severity with first onset or recognition during pregnancy (Metzger et al. 1998). A mild degree of glucose intolerance, triggered by elevated gestational levels of progesterone and placental hormones is a normal occurrence during the late second and third trimester of pregnancy that naturally leads to a rise in blood glucose levels and a subsequent increase in maternal fat deposition and fetal growth (Cordero and Landon 1993, Girling and Dornhorst 1997). In non-GDM pregnancies, pancreatic insulin secretion increases concurrently during the late second and third trimester to compensate for the rise in the mothers' serum glucose levels

(Cordero and Landon 1993). Conversely, in GDM pregnancies, this adaptive pancreatic insulin response is not adequate to maintain normal glycemic levels, either because of insulin insufficiency and/or marked insulin resistance (Persson et al. 1997). As a result, mothers with GDM often tend to maintain elevated serum concentrations of glucose beyond 24-28 weeks of pregnancy, unless controlled by diet and/or insulin therapy (Girling and Dornhorst 1997).

Maternal complications associated with GDM

In addition to maternal hyperglycemia and insulin resistance during pregnancy, other clinical symptoms associated with GDM pregnancies include proteinuria, polydipsia, water retention, hypertension, and pre-eclampsia (Girling and Dornhorst 1997). Most often these maternal complications subside post-partum. In many cases however, subtle manifestations of impaired insulin secretory capacity remain. Women with continuing glucose intolerance post-partum are known to have an increased risk of developing GDM in a subsequent pregnancy and of developing overt type 2 diabetes later on in life. The risk of progression to diabetes within 5 years of the diagnosis of GDM is related to the gestational age at diagnosis, the severity of GDM at diagnosis, the level of hyperglycemia at the first postpartum assessment, the impairment of beta cell function, and the degree of obesity (Metzger et al. 1998). Studies in North American women suggest that GDM mothers have a 35-50% risk of developing type 2 diabetes within 5 years after the index pregnancy (Metzger et al. 1993, MacNeil et al. 2001). In comparison, a study in a Native northern Ontario population found that over 70% of Ojibwa-Cree women with a GDM diagnosis become overtly diabetic within 4 years (Mohamad and Dooley 1998).

Predictors and prevalence of GDM in Native and non-Native populations

Specific predictors of GDM have been identified in recent studies, including pregravid obesity, advanced maternal age, multiparity, a history of GDM in a previous pregnancy and a family history of diabetes (Engelmau et al. 1988, Dooley et al. 1991, Harris et al. 1997, Godwin et al. 1999, Rodrigues et al. 1999b). In addition to these predictors, Native ethnicity has also been recognized as an independent risk factor for GDM (Adams et al. 1998, Rodrigues et al. 1999b). There is growing epidemiological and pathophysiological

evidence to support that Native women are more prone to develop impaired glucose tolerance (IGT) and GDM than non-Native individuals, perhaps due to genetic differences in the way Native individuals metabolize and store glucose in their cells (Langer 1991). The ethnic differences in gestational glucose metabolism are exemplified by the high prevalence rates of GDM in Native populations across North America of 4-14%, compared with rates of 3-5% for the general North American population (Magee et al. 1993, Rith-Najarian et al. 1993, Harris et al. 1997, Rodrigues et al. 1999a). In the Quebec James Bay Cree population specifically, the prevalence of GDM is 12.8%, which is lower than the rate reported for the Zuni Indian population of western New Mexico (14.1%), but higher than rates reported for the Minnesota Chippewa (5.8%) and Ontario Ojibwa-Cree (8.4%) populations (Benjamin et al. 1993, Rith-Najarian et al. 1996, Harris et al. 1997, Rodrigues et al. 1999a). In light of these high prevalence rates of GDM among the James Bay Cree and other Native North American populations, it is important for health professionals to recognize and screen for appropriate GDM risk factors. The predictors of GDM reported for different Native and non-Native populations will be reviewed below.

Pregravid obesity

Obesity has been consistently reported as a significant risk factor for GDM in both Native and non-Native population groups (Berkowitz et al. 1992, Harris et al. 1997, Godwin et al. 1999, Rodrigues et al. 1999b). Obese women are known to have an underlying degree of glucose intolerance that increases their susceptibility to develop GDM during pregnancy (Hollingsworth and Ney 1992). There is also evidence to support an ethnic difference in the overall risk for GDM between obese Native versus obese non-Native women (Rodrigues et al. 1999b). Rodrigues et al. (1999b) found that non-obese (Native and non-Native) women did not have an increased risk of GDM during pregnancy (OR=1.42; 95% CI 0.67-2.71), whereas obese Native women had a significantly higher risk (compared with obese non-Native women) of developing GDM during pregnancy (OR=2.25; 95% CI 1.32-3.80) – indicating an interaction effect between ethnicity and obesity and the risk of developing GDM among Native women (Rodrigues et al. 1999b). The prevalence of obesity among pregnant James Bay Cree women was 51.7% versus

10.0% for non-Native women (Rodrigues et al. 1999b). In comparison, among Ontario Ojibwa-Cree women the prevalence of obesity was 24.6%, and the prevalence of GDM was also slightly lower (8.4%) than the rate for the James Bay Cree (12.8%) (Harris et al. 1997, Rodrigues et al. 1999b).

Advanced maternal age

Harris et al. (1997) hypothesized that blood glucose values rise in some women, particularly Native women, with age, irrespective of weight gain over time, which subsequently increases their risk of developing GDM. In the Ontario Ojibwa-Cree population, over 15% of pregnant women were over 30 years of age, and each five-year increase in maternal age was found to increase the mothers' risk for GDM by a factor of two (OR=2.05; 95% CI 1.55-2.72) after adjusting for other maternal risk factors (Harris et al. 1997). Similar associations between maternal age and GDM risk, after adjusting for parity, pregravid weight, and smoking status (inverse effect), have been reported for James Bay and Swampy Cree populations of northern Quebec and Ontario (Godwin et al. 1999, Rodrigues et al. 1999b). In general, Native women aged 35 years and older appear to have the greatest risk of developing diabetes during pregnancy (adjusted RR=4.1, 95% CI 1.5-11.7; Godwin et al. 1999). In the multi-ethnic study by Berkowitz et al. (1992), the adjusted OR for maternal age was similar to that reported for the Canadian Native populations at 1.63 (95% CI 1.48-1.81). Given these research findings it is evident that advanced maternal age (≥ 35 years) is a significant risk factor for GDM for both Native and non-Native women.

Increased parity

Increased parity is another important risk factor for GDM. Nonetheless, the association between maternal parity and GDM does not appear to be consistent across all population groups. In the multi-ethnic study by Berkowitz et al. (1992), the RR for GDM among mothers with ≥ 3 previous births was 2.17 (95% CI 1.57-3.00). However, after adjusting for other risk factors (maternal age, pregravid weight, race, family history of diabetes) parity was not identified as an independent risk factor for GDM. Similarly, in the James Bay Cree and Swampy Cree populations, the adjusted ORs for GDM for multiparous

women were non-significant (OR=0.85; 95% CI 0.40-1.82 and OR=1.2; 95% CI 0.7-2.3 respectively) (Godwin et al. 1999, Rodrigues et al. 1999b). In contrast, among Ontario Ojibwa-Cree women, the adjusted OR for GDM was 3.18 (95% CI 1.45-6.99) for multiparous women (Harris et al. 1997). These findings suggest that multiparity is a significant risk factor for GDM in some, but not all, population groups after accounting for other risk factors such as pregravid weight and maternal age.

Family history of diabetes

Many studies have suggested genetic mechanisms to explain the clustering of glucose intolerance, specifically type 2 diabetes and GDM, within families (Freinkel 1980). Women with a family history of diabetes have a 2-3 fold higher risk for GDM compared with women without a family history of diabetes (Mestman 1980). In the Swampy Cree population, having a first-degree relative with diabetes incurred a RR of 3.0 (95% CI 1.4-6.1) for GDM (Godwin et al. 1999). Similarly, for Ojibwa-Cree women in the Sioux Lookout Zone, the adjusted OR for mothers with a family history of diabetes was 2.08 (95% CI 1.18-3.64). Family history of diabetes was not reported in previous GDM studies for the James Bay Cree population (Rodrigues et al. 1999b). In the multi-ethnic population study mentioned earlier, Berkowitz et al. found that the adjusted RR for GDM among women with a family history of diabetes was 1.43 (95% CI 1.12-1.83). In general, there appears to be a relatively weak but consistent relationship between GDM risk and family history of diabetes in both Native and non-Native populations.

History of GDM in a previous pregnancy

In addition to the other GDM risk factors described above, women with a history of GDM in a previous pregnancy also run higher risks of developing GDM in subsequent pregnancies than women without a previous history of GDM (Dodds et al. 2000). Recurrent GDM may be related to insufficient postnatal follow-up for glucose intolerance prior to subsequent pregnancy, and/or glucose intolerance carried over from a previous GDM pregnancy. It has been suggested that up to 40% of women with GDM maintain some degree of glucose intolerance post-partum, which can either be mild and unnoticeable, or can later manifest itself as type 2 diabetes (Magee et al. 1993). Among

Ontario Ojibwa-Cree women, the adjusted OR for mothers with a previous history of GDM was 2.76 (95% CI 1.17-6.48) (Harris et al. 1997). Similarly for James Bay Cree women, the adjusted OR for GDM for mothers with a previous history of GDM was 4.46 (95% CI 2.24-9.26) (Rodrigues et al. 1999b). Overall, Ontario Swampy Cree women with a maternal history of GDM in a previous pregnancy had the highest risk (RR=6.4; 95% CI 3.5-11.7) for developing GDM in a subsequent pregnancy (Godwin et al. 1999). It has been suggested that for Native American women, a GDM diagnosis during pregnancy may actually be an indicator of pre-existing, undetected type 2 diabetes (Mohamad and Dooley 1998).

Screening for and detection of GDM

Individuals with one or more of the above-mentioned risk factors for GDM, including all Native women, should ideally be screened for glucose intolerance during the first trimester and then again between the 24-28th week of pregnancy. There is ongoing debate concerning the appropriate glycemic cut-offs that should be used to diagnose GDM, and thus minimize maternal and fetal morbidity (Sermer et al. 1995, Langer and Mazze 1998, Demarini et al. 1985, Bérard et al. 1997). Researchers at the Fourth International Workshop Conference on GDM recommended that the 100 g oral glucose tolerance test (OGTT) be used as the standard method for detecting GDM (Metzger et al. 1998). According to this method, fasting blood glucose levels above 5.3 mmol/L, and one hour and two-hour post-prandial blood glucose levels greater than 7.8 mmol/L and 6.7 mmol/L respectively, should be used to screen for GDM (Metzger et al. 1998). Patients with two or more readings above the cut-off levels are treated as GDM, whereas those with one reading above the cut-off levels are treated as IGT. The 2-hour 75 g OGTT is sometimes used in place of the 100 g test because it is sometimes better tolerated by patients, and requires less waiting time for completion of testing.

Numerous studies have shown that intensive prenatal management of GDM (e.g., daily monitoring of blood glucose levels and dietary intake, and insulin treatment if necessary) can help to reduce the risk of neonatal and long-term complications in the offspring of GDM mothers. These relationships between maternal glycemic control and neonatal

outcomes will be described in part 2 of the literature review following the subsequent discussion of the neonatal complications associated with GDM and macrosomic pregnancies.

Neonatal complications associated with GDM

Neonatal complications of GDM can be attributed, for the most part, to an increased transfer of substrates from the mother to the fetus in conjunction with fetal hyperinsulinism (Persson and Hanson 1998). The "toxic effects" of maternal hyperglycemia on fetal growth and development were first described by Pederson in 1967. According to his theory, elevated levels of serum metabolites (e.g., glucose, free fatty acids, ketone bodies, triglycerides and amino acids) in the diabetic mother trigger increase nutrient transfer to the fetus, which in turn creates a hyperglycemic in utero environment that alters fetal growth and body composition (Pederson 1967, Schwartz et al. 1994). Late in the second trimester of pregnancy, the pancreas of the GDM fetus adapts to the hyperglycemic in utero environment by increasing insulin production, which subsequently leads to fetal hyperinsulinemia (Ogata 1991). The culmination of these metabolic events in utero, in many cases, leads to neonatal hypoglycemia, polycythemia, hyperbilirubinemia, respiratory complications, and/or fetal overgrowth (Sermer et al. 1995, Weintrob et al. 1996, Hod et al. 1991). The following section will describe each of the neonatal complications associated with GDM pregnancies.

<u>Hypoglycemia</u>

Transient neonatal hypoglycemia, caused by a carry-over effect of the fetal hyperinsulinemic state into the neonatal period, develops in approximately 5-24% of GDM offspring, compared with 0-5% of non-GDM offspring (Hod et al. 1991, Jensen et al. 2000). Research has shown that high C-peptide and insulin concentrations in hypoglycemic neonates limit hepatic glucose production, inhibit normal production of gluconeogenic enzymes (e.g., phosphoenolpyruvate carboxykinase), and enhance tissue uptake of glucose (Girard et al. 1977). It is often recommended therefore that infants of pre-diabetic and GDM pregnancies have their capillary blood glucose levels checked at birth and every 2-4 hours thereafter for the first 12-48 hours (or more frequently if a

GDM infant is jittery, unduly sleepy, apneic, feeding poorly, cyanotic or having seizures; Cordero and Landon 1993). Most hypoglycemic infants will respond to early, frequent oral feeds as treatment. However, in some cases more aggressive treatment with oral or intravenous glucose solutions may be required. According to Schwartz, blood glucose levels below 1.7 mmol/L during the first 48 hours, and below 2.2 mmol/L after the first 48 hours indicate neonatal hypoglycemia (1991). Nonetheless, some authors contend that less conservative cut-offs of 3.3 mmol/L (Stanley and Baker 1999) or 2.0 mmol/L (Agrawal et al. 2000) be used to diagnose neonatal hypoglycemia in order to minimize the likelihood of cortical damage and long-term sequelae.

The long-term consequences of unrecognized and/or untreated neonatal hypoglycemia (e.g., seizures and permanent brain injury) are an issue of current debate (Stanley and Baker 1999). Previous studies of outcomes of neonatal hypoglycemia are flawed by factors such as retrospective design and the lack of control for co-existing clinical complications. Hawdon (1999) suggests that the severity and duration of low neonatal glycemic levels required to cause lasting harm to the infant varies between subjects, and is related to the ability of each infant to mount a protective response such as the production of ketone bodies to be used as an alternative fuel source by the brain. To test this theory, Schrier et al. (1990) produced neonatal hypoglycemia of defined duration and severity in newborn rhesus monkeys, and found that neonatal hypoglycemia of 10 hours duration caused more adaptive and developmental difficulties compared with control monkeys. However, in animals with 6.5 hours of hypoglycemia, no deficits in the measures of cognitive abilities or behaviour were observed. These findings indicate that the duration of untreated neonatal hypoglycemia is associated with increased risk of long-term developmental consequences. In contrast, a human study by Persson and Gentz did not identify this same relationship between neonatal glycemic values and long-term impaired physical or neurological development in offspring of GDM pregnancies (1984). A third study on hypoglycemia by Stenninger et al. (1998) reported that children born to mothers with GDM during pregnancy, and who subsequently developed hypoglycemia during the first 24-48 hours of life, had significantly more difficulties in a validated screening test for minimal brain dysfunction than controls, and were also more often

reported to be hyperactive, impulsive, and easily distracted than children born to mothers without GDM.

Given this conflicting evidence concerning the long-term consequences of neonatal hypoglycemia, the lack of prospective studies, and the paucity of information about medical interventions used to treat hypoglycemia in previous research studies, it is difficult to discern whether or not fetal hypoglycemia is truly associated with increased long-term morbidity. Further prospective studies involving long-term follow-up of GDM offspring with hypoglycemia are certainly warranted in order to clarify these issues.

Polycythemia

In addition to neonatal hypoglycemia, polycythemia is a significant neonatal complication of GDM pregnancies, affecting between 7-20% of infants of diabetic offspring compared with 3-5% of infants of non-diabetic mothers (Mimouni et al. 1986, Hod et al. 1995, Ogata 1995). Polycythemia is defined by a hematocrit value greater than or equal to 65% during the neonatal period, and is caused by enhanced haematopoiesis (red blood cell production) in utero, which is triggered by increased erythropoietin production driven by fetal hyperinsulinemia (Widness et al. 1981). There is also evidence to suggest that fetal hypoxia, due to poor maternal glycemic control, can contribute to causing polycythemia in infants of diabetic pregnancies (Widness et al. 1981). Untreated neonatal polycythemia can lead to a "hyperviscosity syndrome" with CNS irritability, worsening of respiratory distress, gastrointestinal disturbances, and kidney damage (Fanaroff et al. 1999). Some practitioners have suggested that early clamping of the umbilical cord may help to minimize the occurrence of neonatal polycythemia, by reducing the amount of maternal blood exchanged with the neonate during the delivery process. However, this hypothesis remains to be confirmed by controlled studies.

Respiratory distress syndrome

Fetal hyperglycemia and hyperinsulinemia have been shown in both animal and clinical studies to effectively delay pulmonary maturation by inhibiting the development of

enzymes necessary for the synthesis of the phospholipid components of lung surfactant (Smith 1984, Bourbon and Farrell 1985, Cordero and Landon 1993). In vitro studies have also demonstrated that elevated neonatal insulin concentrations inhibit lecithin synthesis and impede the timing of glucocorticoid-induced pulmonary maturation (Smith 1984, Engle et al. 1984). A large study by Robert et al. (1976) reported that infants of diabetic mothers have a 4-6 fold increased risk of respiratory distress syndrome (RDS) at each week of gestation until term compared with non-diabetic offspring. Magee et al. (1993) also identified a higher incidence of supplemental oxygen administration to infants of GDM (5.2%) versus non-GDM mothers (3.8%).

On the other hand, more recent studies have demonstrated that the incidence of RDS among GDM offspring is not significantly higher than for infants in the general population. For example, a study by Persson and Hanson (1998) found that the prevalence of RDS among offspring of Swedish mothers was 0.66% compared with 0.55% for non-GDM offspring (GDM diagnosed as 2 hour blood glucose levels $\geq$ 9.0 mmol/L following a 75 g oral glucose tolerance test). Lower rates of RDS in this study are likely related to superior management of blood glucose levels compared to the 2 previous studies. Persson and Hansson (1998) noted that the intensity of treatment might have varied across the study population due to differences in clinical criteria for initiating insulin therapy at various Swedish medical centers. Hod et al. (1991) similarly found a non-significant difference in the prevalence rates of RDS in GDM versus non-GDM offspring (1.3% versus 1.4%).

Hypocalcemia

Early transient hypocalcemia is another recognized complication of diabetic pregnancies that affects approximately 5% of GDM compared with 2-3% of non-GDM infants (Hod et al. 1995, Weintrob et al. 1996). In severe cases, hypocalcemia (defined as total calcium levels below 2.25 mmol/L) can cause jitteriness, apnea, twitching, and convulsions in the newborn infant and should therefore be monitored carefully (Fanaroff et al. 1999). At present, the mechanism explaining the relationship between GDM and hypocalcemia is not entirely clear. Some authors suggest that hypocalcemia develops

secondary to transient functional neonatal hypoparathyroidism during the first 2-4 days of life (Nogushi et al. 1980, Weintrob et al. 1996). Noguchi et al. also showed that hypocalcemia results from functional fetal hypoparathyroidism, which they explain is caused by fetal magnesium depletion secondary to increased maternal urinary losses of magnesium in poorly controlled diabetic pregnancies (1980). Another study by Demarini et al. demonstrated an inverse correlation between maternal glycated hemoglobin concentrations and neonatal hypoglycemia suggesting a relationship between fetal hyperglycemia-hyperinsulinemia and calcium regulation (1985). In most cases, neonatal hypocalcemia can be treated and corrected by administering oral calcium gluconate and/or a single injection of magnesium sulfate; long-term damage from neonatal hypocalcemia is extremely rare (Weintrob et al. 1996).

Hyperbilirubinemia

Hyperbilirubinemia is a common neonatal complication. Clinical definitions of hyperbilirubinemia vary from total bilirubin measurements ≥ 180 μmol/L to ≥ 220 μmol/L (Alpay et al. 2000). Phototherapy is often provided as treatment for hyperbilirubinemia if jaundice is present, and total bilirubin levels rise above 250 μmol/L. There are several different types of neonatal jaundice. The most common is physiological jaundice, which is caused either by isoimmune sensitization or by the inability of the liver to cope with the normal increased neonatal breakdown of red blood cells (Alpay et al. 2000). If left untreated, severe hyperbilirubinemia can result in kernicterus, mental retardation, cerebral paralysis and ultimately death of the neonate (Fanaroff et al. 1999). The exact relationship between neonatal hyperbilirubinemia and maternal GDM has not been discerned. Nonetheless, hyperbilirubinemia remains more common among GDM (16-23%) versus non-GDM (8-15%) offspring (Ogata et al. 1995, Bérard et al. 1998). Some researchers suggest that macrosomic infants of GDM mothers may be more susceptible to develop hyperbilirubinemia because of increased risk of bruising at delivery, thereby augmenting bilirubin production from the breakdown of red blood cells (Fanaroff et al. 1999). However, this hypothesis has not been confirmed by controlled scientific studies.

Macrosomia

Fetal macrosomia is a significant outcome of GDM pregnancies and is also an independent risk factor for additional neonatal birth trauma injuries. Its pathophysiology, risk factors and associated morbidities are reviewed separately in part 2.

Long-term consequences of GDM

There is some research evidence to support that offspring of GDM pregnancies are at increased risk of developing IGT and type 2 diabetes in later life (Silverman et al. 1995, Petry and Hales 2000). Several authors propose that the hyperglycemic in utero environment caused by GDM incurs metabolic aberrations leading to fetal insulin resistance that has long lasting effects on glucose tolerance in offspring (Petry and Hales 2000). Silverman et al. (1995) found that excessive insulin secretion in utero (assessed by amniotic fluid insulin levels) was a strong predictor of IGT in adolescence. In this study, IGT was found in only 3.7% (1 of 27) of adolescents whose amniotic fluid insulin concentrations were normal (≤ 100 pmol/l) versus 33.3% (12 of 36) of those with elevated amniotic fluid insulin concentrations ($P < 0.001$). Logistic regression analyses were used to demonstrate that amniotic fluid insulin concentrations were independently associated with adolescent IGT (adjusted for adolescent body weight). Reports by Buchanan and Kjos (1999) have similarly supported that offspring of GDM mothers are at increased risk for obesity, and elevated glucose levels during childhood and adolescence. Both genetic and intrauterine environmental influences likely to contribute to the glycemic abnormalities in offspring of GDM mothers, however, these metabolic relationships remain to be confirmed by further prospective, controlled studies (Silverman et al. 1991).

LITERATURE REVIEW - PART 2

MACROSOMIA

Introduction

Macrosomia is a term used to describe oversized, overweight, or large for gestational age (LGA) infants. In the scientific literature macrosomia is most often defined either as infant birth weight ≥ 4000 g or infant birth weight ≥ 4500 g, irrespective of gestational age or sex (Magee et al. 1993, Ferber 2000). Alternatively, some clinicians use the definition of birth weight ≥ the 90th percentile for a reference population for a given gestational age (Persson and Hanson 1996, Schwartz and Teramo 1999). There is controversy surrounding which of these clinical designations is most appropriate for defining macrosomia given that there is not a specific threshold at which high birth weight, or birth weight for gestational age, is clearly associated with increased incidence of maternal and/or infant morbidity.

A recent report by Langer states that there is a strong positive correlation between birth weight and gestational age (2000). Nevertheless, research in non-Native populations indicates that only 17-21% of macrosomic infants (≥ 4500 g) are delivered after 41 weeks, meaning that the majority of macrosomic infants are actually delivered at term (Boyd et al. 1983, Bérard et al. 1998). Recent studies in Native populations of Canada, have similarly not identified gestational age as a major predictor of macrosomia, however, exact numbers of macrosomic post-date deliveries have not been reported (Harris et al. 1997, Caulfield et al. 1998, Rodrigues et al. 2000). Thompson (1990) reported that "even after stratifying for birth weight by gestational age, macrosomia was still more common in BC Native infants at all gestational ages, except 42 weeks and over, compared with non-Native infants".

Although it is important to consider gestational age when distinguishing between macrosomic and non-macrosomic neonates, some authors suggest that using a set of normative data obtained from one population to define macrosomia, such as the

definition of birth weight ≥ 90th percentile for gestational age, may not be relevant to all populations since normal birth weights for gestational ages may vary with geography and ethnicity (Persson and Hanson 1998). For example, James Bay Cree infants have distinctively higher average birth weights (240 g heavier than non-Native infants), a low prevalence of LBW (2.3%), and a high prevalence of macrosomia (12% ≥ 4500 g; Armstrong et al. 1998, Rodrigues et al. 2000). It would be beneficial therefore to determine a Cree population specific birth weight cut-off (rather than an arbitrary cut-off based on birth weights and injury rates from another population) that can be used to assist health care professionals in identifying infant deliveries that are at increased risk of incurring a birth trauma injury.

Pathophysiology of macrosomia

The growth and development of the macrosomic fetus is regulated by and dependent upon numerous factors including the maternal uterine environment, the functioning of the placenta, and the availability of nutrients to mother and fetus (Langer 1991). Early in gestation, insulin and insulin growth factors are the main determinants of fetal growth and organ development. Fetal insulin production, initiated between 8-10 weeks gestation, is driven primarily by maternal glucose levels, of which approximately 80% is transferred to the fetus across the placental membrane (Langer 1991). As would be expected, offspring of GDM mothers with poor glycemic control are routinely exposed to higher levels of glucose and insulin in utero which in turn leads to accelerated fetal growth. Research also suggests that the in utero growth of macrosomic fetuses tends to accelerate towards term (e.g., after 38 weeks) whereas the growth of non-macrosomic fetuses is more linear throughout pregnancy (Rydhstrom et al. 1989). For this reason, physicians often recommend that an ultrasound measurement be taken for mothers who are at risk of delivering a macrosomic infant (e.g., mothers GDM) prior to delivery in order to assess maternal and fetal risks for birth trauma injury (Langer et al. 1991).

Research studies also indicate that macrosomic offspring of GDM pregnancies can be distinctively characterized in utero by the elevated growth rates of specific insulin-sensitive tissues including subcutaneous fat, heart and liver (Langer 1991). Brain tissue

growth is not typically affected. As a result, many macrosomic infants of diabetic mothers develop thick upper body skin-folds in comparison to non-diabetic control infants of similar birth weight and birth length (McFarland et al. 1998). The overall effects of these growth patterns can be recognized upon delivery by the relatively larger abdominal circumferences and elevated abdominal to head circumference ratios of macrosomic offspring. Persson and Hanson describe "the classic diabetes fetopathy" as macrosomic, plump, plethoric and cushigoid-looking newborn (1998).

Birth weights of Native and non-Native Canadians

Macrosomia is most commonly seen in offspring of diabetic pregnancies, however, it also occurs in offspring of normal pregnancies due to genetic/parental influences or due to congenital hyperinsulinemic syndromes (Schwartz and Teramo 1999). In the general population, the prevalence of macrosomia defined alternatively as birth weight ≥ 4000 g or as birth weight ≥ 4500 g, is approximately 9-10% and 1-2% respectively (Wollschlaeger et al. 1999, Spellacy et al. 1985). In contrast, prevalence rates of macrosomia (≥ 4500 g) are significantly higher among GDM offspring ranging from 13-19% (Bérard et al. 1998, Gregory et al. 1998). Prevalence rates of macrosomia in many Native Canadian populations are also much higher than for the general population (e.g., 12-37% for macrosomia defined as birth weight ≥ 4000 g and 11% for macrosomia defined as birth weight ≥ 4500 g; Thompson et al. 1990, Dyck et al. 1995, Caulfield et al. 1998, Rodrigues et al. 2000). Prevalence rates of macrosomia for specific Native Canadian populations will be reviewed below.

In British Columbia (BC), Thompson et al. (1990) reported a macrosomia (BW ≥ 4000 g) prevalence rate of 15.9% for the Native population between the years of 1982-1988. Furthermore, macrosomia was 50% more frequent among Natives than non-Natives in BC even after stratification for gestational age (RR 1.47, 95% CI: 1.35-1.59). Dyck et al. (1995) similarly reported that 16.3% of live births in northern Saskatchewan and 12.4% of infants in southern Saskatchewan between 1975-1988 weighed ≥ 4000 g at birth. Moving east to the Sioux Lookout Zone of northern Ontario, Caulfield et al. (1998) reported a macrosomia (≥ 4000 g) prevalence rate of 29.2% for the Ojibwa-Cree. In

Moose Factory Ontario, the prevalence of macrosomia (≥ 4500 g) among Swampy Cree infants was 11.6% (Godwin et al. 1999). Finally, in northern Quebec, the prevalence of macrosomia, defined alternatively as birth weight ≥ 4000 g and birth weight ≥ 4500 g, was 37.4% and 11.4% respectively (Rodrigues et al. 2000). As previously discussed, it is not clear whether these high rates of macrosomia reported in Native Canadian populations are due genetic and/or lifestyle factors, or whether these high prevalence rates are associated with increased maternal or neonatal morbidity.

Predictors of macrosomia

Previous studies have revealed that infant birth weight is influenced by a variety of maternal, as well as fetal constitutional, metabolic, and genetic factors (Okun et al. 1997). Although gestational glucose intolerance and GDM have been implicated in most studies as important predictors of newborn macrosomia (Sermer et al. 1995, Caulfield et al. 1998), other reports have emphasized that other maternal factors, namely maternal obesity, contribute even more significantly to high birth weight outcomes (Okun et al. 1997). It is difficult to identify which specific factors truly contribute to macrosomia given that several of its risk factors (e.g., maternal obesity, excessive weight gain during pregnancy, and increasing maternal age and parity) are the same as those for GDM. Other risk factors for macrosomia include increased maternal height, Native American ethnicity, male infant sex, previous delivery of a macrosomic infant, increased gestational age, and cigarette smoking (inverse effect) (Monroe et al. 1984, Caulfield et al. 1998, Schwartz and Teramo 1999, Langer 2000, Rodrigues et al. 2000).

A recent study by Okun et al. (1997) found that mothers of macrosomic (≥ 4000 g) newborns were significantly heavier (by prepregnancy weight), more obese (by BMI), demonstrated more weight gain during the index pregnancy, and were significantly taller than mothers of non-macrosomic newborns. Multiple logistic regression analyses (adjusted for prepregnancy weight, weight gain, maternal smoking habits, parity, male gender, gestational age, ethnicity, maternal birth weight, maternal height and maternal age) revealed that prepregnancy weight and weight gain were the most significant predictors of macrosomia (≥ 4000 g) with ORs of 1.5 (95% CI 1.3-1.8) and 1.7 (95% CI

1.67-1.78) respectively (Okun et al. 1997). GDM was not a significant predictor of infant macrosomia in this study, however, the authors emphasize that all women with GDM were treated with either diet and/or insulin therapy. As a result, the treatment of mothers with more pronounced carbohydrate intolerance could have masked the true effect of carbohydrate intolerance on infant birth weight in this study (Okun et al. 1997).

Another study by Snyder et al. (1994) looked at predictors of infant birth weight in offspring of mothers with GDM, and found that the predictors of birth weight differed for obese (BMI > 26 kg/m^2) versus non-obese mothers. In obese women she found a significant rise in birth weight (174 g) for every 1 mmol/L rise in postprandial serum glucose, whereas the same 1 mmol/L rise in postprandial serum glucose was associated with a smaller but significant rise in birth weight (85 g) in non-obese women (Snyder et al. 1994). Among overweight and obese women, the main factors that predicted increased birth weight in Snyders' (1994) study were pre-diagnostic rate of weight gain, and fasting or post-prandial serum glucose. Both of these aforementioned studies underscore the importance of normalizing prepregnancy weight and limiting excessive weight gain during pregnancy, in addition to attaining euglycemia, in order to reduce the overall incidence of macrosomia (Snyder et al. 1994, Okun et al. 1997). These studies also emphasize the importance of implementing different management strategies for women with different pregravid weights in order to minimize the incidence of macrosomia.

Among Native Canadian women, GDM and pregravid obesity are also important risk factors for infant macrosomia. In the James Bay Cree population, Rodrigues et al. found that women with GDM were 4.5 times more likely to deliver a macrosomic infant compared with women without GDM, whereas non-Native women with GDM had the same risk for infant macrosomia as normoglycemic non-Native women (Rodrigues et al. 2000). Other significant risk factors for macrosomia in the Cree population were maternal age, multiparity, net rate of weight gain, and smoking status (inverse effect). Another Native birth weight study by Caulfield et al. (1998) in the Ojibwa-Cree population of northern Ontario demonstrated that gestational age (OR=1.53; 95% CI

1.30-1.80) and delivery of a male infant (OR=1.69; 95% CI 1.18-2.42) were the most significant predictors of macrosomia. Similar to the findings of Rodrigues et al. (2000) Caulfield et al. (1998) also found that maternal history of macrosomia, history of GDM, BMI, gestational weight gain, smoking status (inverse effect), and glycemic status (results of oral glucose challenge test and oral glucose tolerance test) were significant predictors of macrosomia. Maternal age was also positively associated with risk of macrosomia, however, it became non-significant after adjusting for maternal history of macrosomia and GDM in a previous pregnancy (Caulfield et al. 1998).

The differences observed between Native and non-Native populations with regards to the involvement of maternal GDM status on birth weight outcomes could potentially reflect differences in medical follow-up and compliance with recommendations regarding diet and/or insulin therapy between the two populations. In the rural Cree population for example, diet and blood glucose monitoring by health care staff, and compliance by patients to abide by recommendations is often poor relative to the more rigid dietary and insulin protocols implemented by health care staff in southern Canadian hospitals. Although there is substantial evidence to support that pregravid obesity, glycemic control, and gestational weight gain are key modifiable risk factors to address in both Native and non-Native populations in order to reduce the overall incidence of macrosomia, diet and exercise intervention programs must be culturally acceptable and relevant in order for them to be effective (Dyck et al. 1999, Special Working Group of the Cree Regional Child and Family Services Committee 2000).

Neonatal birth trauma injuries associated with macrosomia

The main objective of reducing the incidence of macrosomia is to prevent the occurrence of its associated fetal and maternal trauma. Many authors have reported increased rates of shoulder dystocia, clavicular fracture, brachial plexus injury, depressed 5 minute Apgar scores, long delivery intervals, and/or the need for neonatal intensive care unit admission for macrosomic versus non-macrosomic infants. Ultrasound scans are used to predict which fetuses are at risk from trauma at delivery, and caesarean section delivery may be recommended as a means of avoiding birth weight-related complications. The

potential benefit of operative intervention, which carries significant maternal risks, can only be fully determined by understanding the extent and severity of the potential neonatal trauma attributable to the vaginal birth of large infants (Bryant et al. 1998).

Shoulder dystocia

Shoulder dystocia is a complication of macrosomic deliveries, affecting between 10-15% of vaginally delivered infants weighing over 4500 g at birth (Spellacy et al. 1985, Parks and Ziel 1978, Hassan 1988). Shoulder dystocia is recognized when the infant's shoulders fail to be delivered despite standard vaginal delivery manoeuvres due to impaction of the fetus's anterior shoulder on the mother's pubic symphysis (Dodds and Wolfe 2000). In order to facilitate delivery when shoulder dystocia occurs, special obstetric manoeuvres (e.g., the McRobert's manoeuvre, suprapubic pressure, the Wood's corkscrew manoeuvre and/or extraction of the posterior fetal arm), vacuum extraction and/or mid-forceps may be employed by the attending physician. Infant morbidities associated with shoulder dystocia are rare, but include facial nerve palsy (sometimes associated with forceps use), intracerebral haemorrhage, microcephaly, brachial plexus damage, depressed Apgar scores, the need for neonatal intensive care unit admission, and neonatal death (Bérard et al. 1998, Kolderup et al. 1997).

The association between GDM and shoulder dystocia has been widely debated. Several authors argue that although GDM is in the causal pathway of shoulder dystocia (because it is a predictor of macrosomia), it is not a true independent predictor of shoulder dystocia or birth trauma injury (Nocon et al. 1993). The interpretation of different studies comparing the neonatal outcomes of macrosomic versus GDM pregnancies is often confounded by the lack of control variables such as maternal age, parity, and pregravid weight. Nonetheless, some studies that have controlled for maternal age, parity, and pregravid weight, have shown an increased risk of shoulder dystocia associated with GDM (OR 1.7; Nesbitt et al. 1996). Lewis et al. also found that macrosomia ≥ 4000 g (OR=10.9; 95% CI 6.58-17.9), concurrent diabetes mellitus (OR=5.01, 95% CI 1.58-5.0), prior delivery of a fetus ≥ 4000 g (OR=2.38; 95% CI 1.15-4.82), prior shoulder dystocia (OR=11.9; 95% CI 2.08-63.7), and excessive weight gain ≥ 20 kg during pregnancy

(OR=1.74; 95% CI 1.05-2.85) were all significant risk factors for shoulder dystocia (1998). On the other hand, Nocon et al. (1993) analyzed over 12 000 vaginal deliveries and found that although birth weight was significantly associated with increased risk of shoulder dystocia (> 4000 g), maternal obesity, multiparity, post-date pregnancy, episiotomy, and low-forceps delivery had no predictive value on shoulder dystocia outcome. Overall, macrosomia appears to be the most significant predictor of shoulder dystocia. However, in the majority of cases, shoulder dystocia remains an unpredictable event.

Clavicular fracture, brachial plexus injury, and Erb's palsy

As previously mentioned, clavicular fracture and brachial plexus injury are rare, yet significant outcomes of GDM pregnancies and macrosomic deliveries. If shoulder dystocia is not overcome by traction on the fetal head, then special delivery manoeuvres may be attempted by the attending physician in order to displace the anterior shoulder behind the symphis pubis (Faranoff et al. 1999). If these manoeuvres are unsuccessful, then the clavicle or humerus may be fractured in order to allow for delivery of the infant. Although most clavicular fractures can be expected to heal without significant sequelae when they are isolated from other significant injury (Kolderup et al. 1997), it can sometimes result in damage to the brachial plexus system with the possibility of a permanent Erb's palsy (Blickstein et al. 1998). Erb's palsy involves the paralysis of the deltoid and intraspinatus muscles of the infant, as well as the flexor muscles of the forearm, causing the entire arm to fall limply close to the side of the body with the forearm extended and internally rotated (Faranoff et al. 1999). Brachial plexus injury may follow a difficult delivery, but may also follow intrauterine maladaptation or the normal forces of labour and descent with stretching of the involved nerve roots (Hankins and Clark 1995). A meta-analysis study found an increasing incidence of BPI was significantly associated with infant birth weight (Rouse et al. 1996). The prevalence of BPI among infants weighing < 4000 g was 0.9 per 1000 births, compared with 1.8 per 1000 births for infants weighing 4000-4499 g and 2.6 per 1000 births for infants weighing ≥ 4500 g (Rouse et al. 1996). Another recent study evaluated a large group of vaginally delivered neonates weighing more than 4200 g and found the prevalence of

brachial plexus injury to be 1.3% (Blickstein et al. 1998). Overall, clavicular fracture, brachial plexus injuries, and Erb's palsy are rare outcomes that are more common among macrosomic versus non-macrosomic deliveries. Specific maternal and antenatal risk factors for permanent brachial plexus and intraspinus nerve damage have not been identified in previous studies (Rouse et al. 1996).

Delivery method and birth injury among macrosomic infants

Many different studies have looked at method of delivery and incidence of persistent birth injury in non-Native macrosomic infants with equivocal results. The caesarean section rate in the general population ranges from 20-25% (Conway and Langer 1997, Rodrigues et al. 2000). In the James Bay Cree population, the overall rate of caesarean section deliveries is interestingly lower than that of non-Native populations (15.7%) despite their higher rate of infant macrosomia (Rodrigues et al. 2000). Issues of practice style, logistical feasibility of operative delivery, and cultural preference likely influence the lower prevalence rates of caesarean section delivery in this Native population. There is widespread debate concerning the most appropriate method of delivery for macrosomic fetuses, both in diabetic and non-diabetic pregnancies. Whereas some authors recommend elective caesarean at an estimated fetal weight over 4000 g in diabetic patients, others suggest that a weight threshold of 4500 g should be used to reduce unnecessary intervention because of ultrasonographic error (Conway and Langer 1997). In the James Bay Cree population macrosomic infants weighing ≥ 4000 g are not routinely delivered via caesarean section. There has been no indication to date that the low rate of caesarean section delivery in the Cree population is associated with increased maternal or neonatal morbidity and/or mortality.

In a non-Native study, Kolderup et al. (1997) found that macrosomic infants had a six-fold increase in significant birth injuries relative to controls (RR=6.7), and that risk of trauma was correlated with method of delivery (higher rate of injury using forceps versus regular vaginal delivery). The authors of this study advocate a trial of labour and judicious operative vaginal delivery for macrosomic infants (Kolderup et al. 1997). In contrast, a prospective study by Conway and Langer (1997) found that using fetal

ultrasound measurements as an indication for caesarean section delivery in diabetic women helped to reduce the rate of shoulder dystocia without a clinically meaningful increase in caesarean section rate. This research suggests that ultrasonography may be an effective tool for approximating expected birth weight, and that it may be used to determine the need for operative or non-operative deliveries to reduce the incidence of shoulder dystocia (Conway and Langer 1997). On the other hand, other studies have reported that ultrasonography is too inaccurate to be used for determining delivery method, and that far too many caesarean section deliveries would be performed in the hopes of preventing one single shoulder dystocia event in infants weighing less than 5000 g (Bryant et al. 1998).

Relationship between maternal glycemic controls and neonatal outcome

Numerous studies have reported decreased rates of macrosomia, caesarean section delivery, and neonatal complications among offspring of mothers with strict glycemic control during pregnancy (Langer and Mazze 1988, Adams et al. 1998, Sermer et al. 1998). The Summary Report from the Fourth International Workshop Conference on GDM indicates that for strict control, GDM mothers should maintain AC blood glucose levels below 5.3 mmol/L and 1-hour PC blood glucose levels below 7.8 mmol/L throughout pregnancy in order to minimize the incidence of perinatal morbidity (Metzger et al. 1998). A study by Sermer et al. (1995) examined 3637 women with increasing carbohydrate intolerance but without overt GDM. They found that increasing maternal carbohydrate intolerance was an independent predictor of unfavourable pregnancy outcomes including increased incidence of macrosomia 4000 g, caesarean section, pre-eclampsia, phototherapy, and increased length of maternal and neonatal hospital stay. Another study by Adams et al. (1998) found that the incidence of macrosomia, shoulder dystocia, and birth trauma was higher among offspring of mothers with unrecognized versus recognized GDM, independent of maternal obesity and other confounding variables. Together these findings suggest that both the timing and severity of glucose intolerance during pregnancy can have detrimental effects on fetal outcome.

Despite this evidence, some studies on the contrary have reported increased rates of macrosomia and neonatal morbidity despite tight maternal glycemic control (Gabbe et al. 1977, Norlander et al. 1989, Agrawal et al. 2000). One such study recently found that among GDM mothers with strict glycemic control the incidence of early hypoglycemia in infants was still 47% (Agrawal et al 2000). Norlander et al. (1989) similarly report that rates of infant macrosomia were not significantly lower among offspring of mothers with strict versus poor glycaemic control during pregnancy. Some authors also question whether it is possible to reduce neonatal morbidity by tightly controlling maternal glycemic levels without subjecting a patient to long-term hospitalization (Langer and Mazze 1988). Despite this conflicting evidence, researchers at the 4th International Workshop on GDM recently concluded that there is sufficient clinical evidence to support that tight glycemic control can help does help to minimize fetal morbidity, particularly macrosomia (Metzger et al. 1998). Further research is warranted to clarify the extent to which glycemic control can prevent fetal morbidity.

Long-term consequences of macrosomia

There is widespread interest in, and debate over, the long-term associations between birth weight, obesity, and chronic disease (e.g., type 2 diabetes and cardiovascular disease). Several retrospective studies have demonstrated that both LBW and in some cases, high birth weight, individuals are significantly more likely than normal weight individuals to develop type 2 diabetes, and ischemic heart disease, together referred to as “syndrome X” (Barker 1992, Lucas et al. 1999). Opponents of this theory argue that it is too difficult to accurately assess this relationship using retrospective research designs because of the numerous interrelated lifestyle factors that are involved in the etiology of “syndrome X”. Advocates of this theory suggest that in utero metabolic programming is involved in determining whether or not an individual will develop diabetes, and/or ischemic heart disease in later life (Barker 1992). Further prospective studies with longitudinal follow-up are warranted in order to determine the physiological mechanisms by which birth weight may be linked with chronic disease.

High birth weight has also been considered in recent research investigations as potential risk factors for childhood obesity, given that incidence rates of childhood and adolescent onset obesity have risen considerably in both Native and non-Native populations over the past decade. A study by Seidman et al. (1998) found that the risk of adolescent overweight was significantly increased among macrosomic infants, however, macrosomia among infants of diabetic mothers had little predictive value for overweight in adolescence. In further support of this theory, a recent study by Hediger et al. (1999) found that large for gestational age infants remain longer and heavier through 83 months of age, and may be prone to an increasing accumulation of fat in early childhood. A methodological weakness of these studies that have investigated associations between birth weight and growth patterns is that they did not consider dietary intake. In the future, prospective controlled studies that account for infant diet and breastfeeding are warranted to investigate the development of adiposity in macrosomic offspring of GDM and non-GDM offspring.

RESEARCH OBJECTIVES

The objectives of this retrospective chart review study were to: (1) compare prevalence rates of neonatal birth trauma injury (shoulder dystocia, clavicular fracture, brachial plexus injury, Erb's palsy), metabolic complications (hypoglycemia, polycythemia, hypocalcemia, RDS), and caesarean section delivery between macrosomic and non-macrosomic births, and between infants born to mothers with and without GDM for the James Bay Cree population of northern Quebec, and (2) to identify a high birth weight cut-off that can serve as a marker for health care professionals who work in the Cree communities to assist them in identifying deliveries at increased risk of birth injury and metabolic complications.

METHODOLOGY

Background: the James Bay Cree population

The Cree of the Eeyou-Istchee region of eastern James Bay are a small but growing Native Canadian population (n=11 500) with approximately 50% of its people under 20 years of age, and an annual birth rate of approximately 325 births per year (Lavallée et al. 1991). The Cree population is spread across four inland (Mistissini, Nemaska, Oujebougamau, and Waswanipi) and five coastal villages of northeastern Quebec (Chisasibi, East Main, Waskaganash, Wemindiji, and Whapsmagoustou). Health care facilities, staffed primarily by nurses (and some by physicians also), are located in each community. The majority of expecting Cree mothers are transported to hospital centres in either Val d'Or or Chibougamau two to three weeks prior to delivery. Low-risk, non-operative deliveries for women from the coastal Cree communities are managed at the Chisasibi Hospital. High-risk Cree deliveries are transported to hospitals in Montreal (e.g., Royal Victoria Hospital, Jewish General Hospital), Val d'Or, or Chibougamau.

Data collection and ethical approval

A retrospective chart review procedure was used to collect data for this research project. The primary researcher reviewed mother and infant chart information for all James Bay Cree infants born between January 1st, 1994 and December 31st, 1999. For 8 weeks between December 1999 and July 2000 she travelled to each of the nine James Bay Cree villages, as well as to hospital establishments in Val d'Or and Chibougamau, to independently review over 3000 mother and infant chart records at the community health clinics. The CBHSSJB provided ethical approval for the data collection process. In addition to obtaining permission from the CBHSSJB, the primary researcher requested and obtained ethical approval from the directors of professional services at hospital centres in Chisasibi, Chibougamau, and Val d'Or. Ethics approval for the infant and maternal chart review procedure was also obtained from McGill University. Financial support for travel costs to and from the Cree communities was provided in part by the Cree Board of Health and by the Northern Scientific Training Program.

Infant characteristics and neonatal morbidity

Neonatal records for all singleton deliveries with birth weight > 2500 g were included in the study. Cases of maternal pregestational diabetes and glucocorticoid therapy were excluded. Charted measurements of birth weight in grams, length in centimeters, head and thoracic circumferences in centimeters, gestational age in weeks, and Apgar score (using the regular scale of 1-10) were recorded for each infant. Gestational age estimations were based on fetal ultrasound measurements taken between 18–24 weeks, however, in cases where ultrasound data were not available, dates determined by the mother's last menstrual period (LMP), as documented by the attending physician, were accepted. The method of infant delivery was noted as either vaginal (e.g., unassisted, assisted with forceps, assisted with vacuum extraction) or caesarean section. All physician and nurse chart notes as well as laboratory reports for each infant delivery were reviewed up to the infants 30th day of life where possible in order to check for diagnoses of infant morbidity (e.g., shoulder dystocia, clavicular fracture, brachial plexus injury, Erb's palsy, hypoglycemia, polycythemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, respiratory distress syndrome, birth asphyxia) and to document hospital care administered (e.g., phototherapy treatment, oxygen therapy in delivery room, duration of hospital stay).

Birth weight data were entered into the database in raw form. LBW was defined as birth weight ≤ 2500 g. Macrosomia was defined alternatively as birth weight ≥ 4000 g, ≥ 4500 g, and ≥ 5000 g. Birth weights between 2500 g and 3999 g (or 4499 g, or 4999 g) were considered as the control range. Optimal pregnancy outcomes are typically associated with birth weights in the range of 3000-4000 g, however, in order to avoid excluding more subjects than necessary, infants weighing between 2500 g and 2999 g were also included in the "normal" range. Metabolic complications and birth trauma injuries were defined using set cut-offs (see below), and were coded as either yes or no. If an infant had more than one injury (e.g., shoulder dystocia and Erb's palsy), then the infant was included in the group associated with its most serious injury (in this case Erb's palsy). If an infants chart completely lacked physician documentation about birth injury and metabolic complications then the missing variables (e.g., shoulder dystocia, clavicular

fracture, hypoglycemia, polycythemia) were coded as "99". When physician documentation indicated that there were no birth injuries or metabolic complications (e.g., "healthy baby/no complications") and laboratory information was unavailable for the delivery, then the available information was recorded in the database, and the infant was assumed NOT to have any remaining birth trauma or metabolic complications. It was necessary for the primary researcher to make these coding assumptions regarding missing data due to the retrospective nature of the study design, and the fact that only a small percentage of infants are tested for metabolic complications based on clinical indications during the neonatal period. For example, if shoulder dystocia, clavicular fracture, BPI, or Erb's palsy were not documented on either the infant discharge summary or the obstetrical delivery form, which stated that there were "no complications", then the infant was assumed NOT to have involved a birth trauma injury. Similarly, infants who were not screened specifically for hypoglycemia, polycythemia, RDS, hypocalcemia, and hypomagnesemia, were assumed NOT to have had these complications, unless otherwise indicated on the infants discharge summary or physician/nurse forms.

Hypoglycemia was defined as a blood glucose reading below 2.2 mmol/L using peripheral venous blood (Stanley and Baker 1999). Polycythemia was defined by a hematocrit reading ≥ 65% using peripheral venous blood (Mimouni et al. 1986). Hypocalcemia was defined as a total calcium level of ≤ 2.25 mmol/L during the first 24 hours of life, ≤ 1.75 during 24-28 hours of life, and ≤ 2.20 mmol/L after the first 48 hours of life (Demarini et al. 1985). Hyperbilirubinemia was defined by a total bilirubin value greater than 180 μmol/L persisting beyond the two days of life (Mimouni et al. 1986). Phototherapy treatment was also documented (yes/no) for each infant. Oxygen therapy in the delivery room was also recorded (yes/no).

Maternal obstetric history and GDM status

In addition to documenting neonatal/perinatal information of Cree infants, the primary researcher also inspected the chart records of each Cree mother who delivered during the study period. Obesity was defined as pregravid weight > 77 kg. This cut-off corresponds

with a BMI of 29 kg/m^2 for a woman of average stature (1.6 m for Cree women) recommended as the obesity cut-off by the Institute of Medicine (Institute of Medicine 1990, Rodrigues et al. 2000). Pregravid weight information for Cree women was based on the first available weight documented in the patient chart prior to 20 weeks gestation. Height was either measured by the physician or based on maternal reporting. Information on parity and smoking status were based on maternal report. Smoking was defined as any cigarette smoking during pregnancy. The degree of laceration (e.g., 1st, 2nd, 3rd, or 4th degree tear) during delivery was also noted for each mother based on physician documentation on obstetrical delivery forms. In addition, gestational diabetes status was determined by reviewing the laboratory results and physician/nurse notes concerning glucose tolerance tests carried out during the pregnancy under review.

The two-step diagnostic criterion of the National Diabetes Data Group (NDDG) was used to assess the GDM status of the Cree mothers. According to this criterion, Cree women with a positive screen (> 7.8 mmol/L) on their initial 50 g oral glucose challenge test (OGCT) proceed to the 3 hour, 100 g OGTT after an overnight fast. Women with two or more positive screen values for their OGTT are diagnosed with GDM. Women with only one positive value for their OGTT are diagnosed with IGT. Positive values for the OGTT are defined as a fasting value ≥ 5.3 mmol/L, a 1 hour value ≥ 7.8 mmol/L, and a 2-hour value ≥ 6.7 mmol/L. Patients who were labelled as GDM by their attending physician, but were lacking the appropriate laboratory documentation to support the diagnosis were categorized as “missing information”. Data entry codes were used to enter maternal chart information to distinguish mothers with normal glucose tolerance (e.g., code = 1) from those with GDM (e.g., code = 2), IGT (e.g., code = 3), a high screen on their OGCT but no OGTT (e.g., code = 4), pregestational diabetic (e.g., code = 5), and those who were missing information about their glycemic status (e.g., code = 6).

STATISTICAL ANALYSES

The prevalence of adverse pregnancy outcomes was compared between macrosomic infants (defined alternately as birth weight ≥ 4000g and birth weight ≥ 4500 g) and non-macrosomic infants (2500 g to 3999 g or 2500 to 4499 g) using independent chi-square analyses and the Fisher's Exact test. The prevalence of adverse pregnancy outcomes was also compared between GDM and non-GDM subjects. In addition, differences between continuous variables for macrosomic versus non-macrosomic and for GDM versus non-GDM subjects were compared using the Student's independent t-test. The main dependent variables included overall birth injury, shoulder dystocia, clavicular fracture, BPI, Erb's palsy, hypoglycemia, polycythemia, hypocalcemia, hyperbilirubinemia, RDS, caesarean section delivery, hospital stay > 3 days, and 5 minute Apgar score < 7. Independent variables included birth weight, length, head and thoracic circumferences, gestational age, maternal age, parity, pregravid weight, and glycemic status.

The effect of infant macrosomia on three major outcomes was determined in univariate and multivariate analyses: (1) birth injury, including shoulder dystocia, clavicular fracture, brachial plexus injury, BPI, Erb's Palsy, (2) metabolic complications, including hypoglycemia, polycythemia, hypocalcemia, hyperbilirubinemia, RDS, and (3) caesarean section delivery. Multiple logistic regression analyses were used to estimate adjusted ORs and 95% confidence intervals, and to determine the independent and combined effects of infant macrosomia and GDM on each neonatal outcome after adjusting for maternal age, parity, pregravid body mass, and gestational age at delivery. All analyses were conducted using the Statistical Processor Software System™ (SPSS, version 8.0).

RESULTS

Study Population

Infant birth and maternal information was compiled for all 1914 James Bay Cree infants delivered between January 1994 and December 1999. Prior to the main data analysis, 45 LBW (≤ 2500 g) and 45 twins/triplets were excluded from the data set (see figure 1). In addition, 15 infants were excluded because their mothers had pregestational diabetes. Moreover, 159 infants were excluded because of missing birth weight (n=27) or birth complication information (n=132), leaving 1650 infants for inclusion in the statistical analyses. The birth weights of both the included and excluded subject populations were normally distributed (see figures 2 & 3, table 1). Student's independent sample t-tests revealed that overall, the excluded subject group (n=159) did not differ significantly from the rest of the study population in terms of mean birth weight, parity, mother's age, or pregravid weight (see table 2). However, the excluded group of subjects did have a shorter mean gestational age compared with included subjects (38.9 wks vs. 39.2 wks; $p<0.01$).

Subjects

The average birth weight among the James Bay Cree population was 3844 ± 511 g (n=1650). The average gestational age was 39.2 ± 1.3 weeks (table 2). The prevalence of infant macrosomia defined alternatively as absolute birth weight ≥ 4000 g or ≥ 4500 g or ≥ 5000 g was 36.0% and 10.4% and 1.9% respectively. Overall, 85% of the infants were delivered vaginally and 15% were delivered via caesarean section. Of the 1388 vaginal deliveries, 4.9% (n=68) involved the use of forceps and 4.2% (n=58) involved the vacuum suction delivery method (table 3). The use of forceps, vacuum, and caesarean section delivery methods was significantly more common among macrosomic (≥ 4500 g) versus non-macrosomic infants ($p<0.05$) (table 3). The majority (54.5%) of Cree infants were delivered at the Centre Hospitalier de Val d'Or (n=899), and the remaining infants were delivered in Chibougamau (n=484), Chisasibi (n=199), or in hospitals outside of the James Bay region (n=49). Information about birth hospital location was missing from the charts of 19 subjects.

General maternal characteristics for the study population are reported in table 2. The average age of the Cree mothers was 24.0 ± 5.6 years. Thirty-two percent were nulliparous, 24% were primiparous, 40% were multiparous, and 4% were grand-multiparous (parity ≥ 5). Data on pregravid weight and height were not recorded systematically in patient charts. Using available data, the average pregravid weight was 80.7 ± 17.3 kg (n=969) and the average body mass index (BMI) was 31.7 ± 7.1 kg /m^2 (n=241). The prevalence rate of obesity (> 77 kg) among pregnant Cree women was 54.2% (n=525/969) (Institute of Medicine 1990). This rate was substantially higher among GDM mothers (71.6% versus 52.0% for non-GDM mothers). With respect to smoking status, 57.7% of Cree women were non-smokers, 38.0% smoked less than 10 cigarettes per day, and 4.3% smoked ten or more cigarettes per day.

Prevalence of GDM

Results of prenatal OGCTs and OGTTs were collected for 1379 Cree mothers in order to assess the prevalence of GDM in the population (see table 4). Of the mothers whose charts were reviewed for GDM status, 13.8% (n=190/1379; 95% CI 12.0-15.6) tested positive for GDM and 8.9% (n=123/1379; 95% CI 7.2–10.6) were diagnosed with IGT. Another 11.3% (n=156/1379; 95% CI 9.6–13.0) of women had 1-hour OGCT values ≥ 7.8 mmol/L but failed to receive a 100 g OGTT after an overnight fast to confirm their diabetes status. The positive predictive value (PPV) of the OGCT screen test was used to estimate the potential number of cases of GDM among women who were given an OGCT but did not undergo the OGTT. A PPV of 26% was used as previously established by Rodrigues et al. for the James Bay Cree population (1999a). The use of this proportion to estimate potential cases of GDM increased the GDM prevalence estimate from 13.8% to 16.6%. Reasons for no OGTT following a high screen were patient refusal, missed laboratory appointments, physician diagnosis of GDM based only on a positive screen value, or missing OGTT values from patient chart records. In addition, 271 Cree mothers (out of 1650) were either not screened at all for GDM during pregnancy or their GDM status was not recorded by the data collectors due to patient absence at laboratory

appointments, lack of documented prenatal follow-up, missing patient charts or failure by the data collectors to locate patient information during the data collection period.

Characteristics of macrosomic births

Independent t-test analyses showed that infants with birth weights ≥ 4000 g or ≥ 4500 g were significantly longer at birth ($p<0.01$), had larger head and thoracic circumferences ($p<0.01$), greater thoracic to head circumference ratios ($p<0.01$), and longer gestation periods ($p<0.01$) than non-macrosomic infants. The proportion of post-date infants (> 41 weeks) was significantly higher among macrosomic ≥ 4000 g (3.9%) versus non-macrosomic (1.0%) infants ($p<0.01$). On the other hand, when macrosomia was defined as birth weight ≥ 4500 g, the difference between macrosomic and non-macrosomic groups for post-datism did not reach statistical significance (one-sided p-value = 0.056). Mothers of macrosomic infants weighing ≥ 4000 g or ≥ 4500 g tended to have higher pregravid weights ($p<0.05$) and higher parity ($p<0.05$) than mothers of non-macrosomic fetuses. Moreover, macrosomic infants ≥ 4000 g had significantly older mothers than non-macrosomic infants (one-sided p-value = 0.05; non-significant for infants weighing ≥ 4500 g). A comparison of infant and maternal characteristics of macrosomic versus non-macrosomic infants is presented in table 5. In multivariate analyses, pregravid weight and GDM were the only significant predictors of macrosomia ≥ 4500 g for Cree women (table 6).

Delivery method and duration of hospital stay

Caesarean section, unassisted vaginal and assisted vaginal delivery (e.g., forceps or vacuum extraction) rates for macrosomic and non-macrosomic deliveries are presented in table 3. The proportion of caesarean section deliveries was significantly higher among infants weighing ≥ 4500 g than among normal weight infants ($p<0.01$). This difference was not significant when macrosomia was defined as birth weight ≥ 4000 g. After adjusting for infant birth weight, gestational age, maternal age, and parity, pregravid obesity (≥ 77 kg) was the only independent predictor of caesarean section delivery among Cree women (OR=1.74; 95% CI 1.22-2.50). Caesarean section deliveries were not more

common among diabetic pregnancies (p=0.09). Of the vaginal deliveries ≥ 4000 g, 12.7% required the use of forceps or vacuum compared with 7.1% of non-macrosomic vaginal deliveries (p<0.01). This finding was not significant for deliveries ≥ 4500 g. With respect to hospital stay, macrosomic infants were significantly more likely than non-macrosomic infants to spend ≥ 3 days in hospital post-delivery (p<0.01 for birth weight ≥ 4000 g, or ≥ 4500 g). Peritoneal tearing ($3^{rd}/4^{th}$ degree tears) was also significantly more common among mothers who gave birth to macrosomic versus non-macrosomic infants (p<0.05 for birth weight ≥ 4000 g; non-significant for birth weight ≥ 4500 g). The prevalence of $3^{rd}/4^{th}$ degree tears was 3.1% among infants weighing < 4000 g at birth versus 12.5% among infants weighing ≥ 5000 g at birth.

Macrosomia among GDM pregnancies

Macrosomia was significantly more common in GDM versus non-GDM pregnancies (p<0.01 for macrosomia defined as either birth weight ≥ 4000 g or ≥ 4500 g). Out of 190 GDM pregnancies, 62 (32.6%) resulted in delivery of an infant weighing 4000-4499 g and 38 (20%) resulted in delivery of an infant weighing ≥ 4500 g. On the other hand, out of 910 mothers with normal glucose tolerance, 76 (8.4%) delivered macrosomic infants ≥ 4500 g. The overall prevalence rate of macrosomia (≥ 4500 g) among offspring of normal glycemic mothers was 4.6% (76/1650). Prevalence rates of GDM per infant birth weight category (< 4000 g, 4000-4499 g, and ≥ 4500 g) are presented in table 7. In this table, we see that 10.2% of infants in the birth weight < 4000 g category versus 17.5% in the 4000-4499 g category, and 27.3% in the ≥ 4500 g category, had mothers with GDM. Conversely, 69.5% of infants in the birth weight < 4000 g category versus 61.7% in the 4000-4499 g category, and 54.7% in the ≥ 4500 g category, had mothers with normal glucose tolerance. Chi-square tests indicated that higher birth weight infants (< 4000 g versus 4000-4499 g versus ≥ 4500 g categories) were not more common among mothers with IGT (p > 0.05) or among mothers with a high screen no OGTT (p > 0.05).

Birth trauma injuries

During the study period there were 42 documented neonatal cases of shoulder dystocia, 15 cases of clavicular fracture, 4 cases of brachial plexus injury, and 2 cases of Erb's Palsy in the Cree population. Infants that experienced more than one birth trauma injury (e.g., shoulder dystocia and clavicular fracture) were classified according to their most severe injury (in the above case, clavicular fracture). In total there were 7 infants with more than 1 birth trauma injury (see table 8 for a description of the birth characteristics of these infants). There were also 2 humeral fractures, 1 case of facial paralysis, 1 calf paralysis, and 13 cranial haematomas. Cranial haematomas were most commonly associated with forceps and vacuum delivery techniques ($p<0.01$), and were more common among macrosomic (≥ 4500 g) versus non-macrosomic deliveries ($p<0.05$). The overall prevalence of birth trauma injury (excluding cranial haematomas) among Cree newborns was 4.1%, and the prevalence rate of shoulder dystocia and clavicular fracture was higher among infants weighing ≥ 4500 g at birth compared with those weighing < 4000 g and 4000-4499 g at birth ($p < 0.05$; table 9). The overall rate of birth trauma injury (excluding cranial haematomas) rose from 1.3% among births < 4000 g, to 5.7% among births 4000-4499 g, to 16.9% among births ≥ 4500 g ($p > 0.05$). In multi-variable analyses, macrosomia ≥ 4500 g (OR=8.60; 95% CI 3.55-19.19) and maternal obesity (> 77 kg; OR=2.84; 95% CI 1.04-7.74) were significant predictors of birth trauma injury. Macrosomic infants with birth weights ≥ 4500 g were not significantly more likely to have 5 minute Apgar scores < 7 than non-macrosomic infants ($p > 0.05$ using birth weight ≥ 4000 g or birth weight ≥ 4500 g). Specific birth trauma injuries and their relationships to macrosomia and GDM are summarized in tables 10 and 11.

<u>Shoulder dystocia</u>

Of the 42 documented cases of shoulder dystocia during delivery, 6 cases were noted among normal birth weight infants, 20 among macrosomic infants weighing between 4000 g to 4499 g and 16 among macrosomic infants weighing over 4500 g. The average birth weight of the infants with shoulder dystocia was 4449 ± 517 g. Only six cases of shoulder dystocia were noted among GDM offspring, and all cases of GDM-shoulder dystocia involved macrosomic (≥ 4000 g) offspring. The prevalence of shoulder dystocia

was not significantly higher among infants of GDM (3.2%) versus non-GDM (2.5%) pregnancies. Multiple logistic regression analyses revealed that macrosomia (≥ 4500 g) and pregravid obesity (> 77 kg) were significant predictors of shoulder dystocia (OR=6.75; 95% CI 2.83-16.09 and OR=3.18; 95% CI 1.05-9.60 respectively). The prevalence of shoulder dystocia was 7.1% among infants weighing 4500-4999 g compared with 18.1% among infants weighing ≥ 5000 g at birth.

Clavicular fracture

Of the 15 cases of clavicular fracture, 2 cases occurred among infants weighing between 4000 g and 4499 g and 10 cases occurred among infants weighing over 4500 g. Only 3 cases of clavicular fracture were noted among non-macrosomic infants. The average birth weight of the infants with clavicular fracture was 4612 ± 581 g, and the prevalence of clavicular fracture was significantly higher for GDM (2.6%) versus non-GDM (0.7%) pregnancies (Fisher's Exact test, p=0.02). Multiple logistic regression analyses revealed that GDM was a significant predictor of clavicular fracture (OR=3.92; CI 1.33-11.56), however, after adding macrosomia into the equation, GDM became non-significant. Infant macrosomia (≥ 4500 g) was therefore the only independent predictor of clavicular fracture (OR=18.18; 95% CI 6.14-53.82). The prevalence of clavicular fracture was 0.5% (2/423) among infants weighing 4000-4499 g (6/140) at birth versus 4.3% among infants weighing 4500-4999 g versus 12.1% (4/32) among infants weighing ≥ 5000 g.

Brachial plexus injury

In total there were only 4 documented cases of brachial plexus injury among the Cree during the study period. The birth weights of these 4 infants were 3660 g, 4350 g, 5195 g, and 5330 g. The Fisher's Exact test was used to show that the proportion of macrosomic infants (BW ≥ 4500 g) with BPI (0.6%) was greater than the proportion of non-macrosomic infants with BPI (0.1%) (p=0.056). The difference in the proportion of GDM versus non-GDM offspring with BPI was not significant (Fisher's Exact test, p=0.61) since none of the 4 infants with BPI were the product of a GDM pregnancy. Logistic regression analyses showed that macrosomia (≥ 4500 g) was an independent predictor of BPI (OR=8.68; 95% CI 1.22-62.01).

Erb's Palsy

Two infants in the Cree population were diagnosed with Erb's Palsy during the neonatal period. One infant weighed 3700 g and the other weighed 5330 g at birth. The glycemic status of the 3700 g infant's mother was normal, whereas the 5330 g infant's mothers OGCT reading was elevated. This mother did not receive an OGTT to confirm her GDM status. Interestingly, birth length was a significant predictor of Erb's Palsy (OR=1.53; CI 1.02-2.30) after adjusting for other variables including maternal pregravid weight, age, parity, and infant birth weight. Macrosomia (defined either as birth weight ≥ 4000 g or ≥ 4500 g) was not a significant predictor of Erb's Palsy.

Metabolic complications

Among the Cree population the overall prevalence rate of hypoglycemia was 8.8%, hyperbilirubinemia 28.7%, polycythemia 1.7%, hypocalcemia 0.4%, hypomagnesemia 0.1%, respiratory distress syndrome 2.4% and meconium aspiration 0.5%. Specific metabolic complications and their relationships to macrosomia and GDM are summarized in tables 10 and 11 respectively.

Hypoglycemia

A total of 144 cases of neonatal hypoglycemia were documented between January 1994 and December 1999. Hypoglycemia was significantly more common for macrosomic infants (17.5%) versus non-macrosomic infants (3.8%) (Fisher's Exact test; $p<0.01$). Hypoglycemia was also significantly more common for GDM (18.1%) versus non-GDM (7.6%) associated pregnancies (Fisher's Exact Test, $p<0.01$). Adjusted multiple logistic regression analyses indicated both GDM (OR=2.34; CI 1.52-3.60) and macrosomia ≥ 4500 g (OR=3.30, CI 2.17-5.01) were significant predictors of neonatal hypoglycemia.

Hyperbilirubinemia

The prevalence of hyperbilirubinemia was 30.6% (129/421) in the birth weight 4000-4499 g category, versus 33.6% (47/140) in the 4500-4999 g category versus 37.5% (12/32) in the birth weight ≥ 5000 g category. The prevalence rate of phototherapy

treatment for hyperbilirubinemia however was 10.2% (43/421) in the birth weight 4000-4499 g category, versus 7.9% (11/140) in the 4500-4999 g category, versus 9.4% (3/32) in the birth weight ≥ 5000 g category. The Fisher's Exact test detected significant differences in the percentages of hyperbilirubinemia for macrosomic (BW ≥ 4000 g) and non-macrosomic infants (p=0.02). The difference was also significant when macrosomia was defined as birth weight ≥ 4500 g (p=0.05). Nonetheless, macrosomic (≥ 4500 g) infants were not more likely than non-macrosomic infants to receive phototherapy treatment for hyperbilirubinemia. Furthermore, hyperbilirubinemia was not more common with GDM versus non-GDM offspring (p=0.17). Adjusted logistic regression analyses indicate that macrosomia defined as birth weight ≥ 4000 g (OR=1.26; CI 1.01-1.57), but not maternal GDM status, was an independent predictor of hyperbilirubinemia among Cree infants.

Polycythemia, hypocalcemia, hypomagnesemia, RDS and meconium aspiration

The prevalence of polycythemia was significantly higher among GDM (3.7%) versus non-GDM (1.4%) offspring (Fisher's Exact test; p=0.03) but was not related to birth weight. Adjusted multiple logistic regression analyses showed that maternal GDM status was the strongest predictor of polycythemia (OR=2.91; CI 1.26-6.70). Hypocalcemia was also more common with GDM (1.6%) versus non-GDM (0.3%) offspring (adjusted OR=5.35, CI 1.20-24.08). Hypomagnesemia, RDS and meconium aspiration were not related to birth weight or maternal GDM status (Fisher's Exact test; p > 0.05). Overall, 22.7% versus 30.2% of non-macrosomic and macrosomic (≥ 4000 g) received oxygen therapy in the delivery room following delivery (Fisher's Exact test, p<0.01), and offspring of GDM pregnancies were more likely to receive oxygen therapy in the delivery room (30.9%) than non-GDM offspring (24.7%; one-sided p-value < 0.05).

DISCUSSION

Birth trauma injury

Previous studies in non-Native North American populations have reported that increasing birth weight predisposes infants to difficult delivery, birth trauma, and increasing rates of neonatal injury (Boyd et al. 1983, Kolderup et al. 1997), and that maternal GDM predisposes increased incidence of metabolic complications, such as hypoglycemia, polycythemia and hypocalcemia (Langer et al. 1991, Persson and Hanson 1998). The present study presents valuable new information about the neonatal health outcomes of a Native Canadian population in light of their elevated prevalence rates of both macrosomia and GDM. The overall prevalence of birth trauma injury (including shoulder dystocia, clavicular fracture, BPI, Erb's palsy, humeral fracture, facial and calf paralysis) among the James Bay Cree population was 1.3% for normal weight deliveries versus 5.7% for macrosomic deliveries ≥ 4000–4499 g and 16.9% for deliveries ≥ 4500 g. In comparison a large US cohort study by Kolderup et al. (1997) reported a much lower injury rate of 0.35% among normal weight deliveries versus 1.6% for macrosomic deliveries ≥ 4500 g. Another Swedish study by Wikstrom et al. (1988) reported injury rates of 0.6% for normal weight infants versus 8.0% for macrosomic deliveries ≥ 4500 g (1988). With respect to specific neonatal injuries among the James Bay Cree, the most common complication was shoulder dystocia. The overall prevalence of shoulder dystocia (2.5%) in the James Bay Cree population was higher than that reported earlier for the Ontario Swampy Cree population (1.8%) (Godwin et al. 1999), and for other non-Native US populations (0.2-2.0%) (Sandmire et al. 1988). However, the low overall prevalence of Erb's palsy in our study (0.1%) was similar to rates reported for other non-Native populations at 0.13-0.81% (Boyd et al. 1983, Bryant et al. 1998).

In the James Bay Cree population, macrosomia (≥ 4500 g) was an independent predictor of shoulder dystocia, clavicular fracture, and brachial plexus injury. Although GDM was a significant predictor of clavicular fracture on its own, it became non-significant when macrosomia (≥ 4500 g) was added to the logistic regression equation. Several previous research investigations have similarly attempted to define risk factors for shoulder

dystocia. Although some studies have reported that birth weight, GDM, gestational weight gain, and/or ultrasound measurements of shoulder and head circumference are important predictors of shoulder dystocia that may be used to assess whether caesarean section delivery is warranted (Lewis et al. 1998, Nesbitt et al. 1998), other studies report that infant macrosomia (≥ 4500 g) is the only consistent predictor of shoulder dystocia (Nocon et al. 1993, Blickstein et al. 1998). Langer et al. (1991) suggest that ultrasound technology is a useful tool for estimating fetal measurements (e.g., weight, head and chest circumference) in utero. The overall benefit of using fetal birth weight measurements and maternal risk factors (e.g., GDM, obesity, previous delivery of a macrosomic infant) to predict the risk of shoulder dystocia outcome and other infant morbidity remains questionable given that approximately 90% of macrosomic deliveries (≥ 4500 g) do not incur a shoulder dystocia event.

There is evidence that birth weight lies in the causal pathway between GDM and shoulder dystocia. Godwin et al. (1998) found that shoulder dystocia was 3 times more likely to occur during deliveries by Swampy Cree women with GDM than by those without GDM, however, controlling for birth weight tended to attenuate this association. In contrast, Nesbitt et al. (1998) reported that gestational diabetes increased the risk of shoulder dystocia by more than 70% (OR=1.71) even after controlling for birth weight, assisted delivery, and other factors. Adams et al. (1998) examined the differences in neonatal outcome between groups of treated and untreated GDM pregnancies and found that unrecognized GDM, but not diet or insulin treated GDM, was a significant risk factor for shoulder dystocia and birth trauma independent of maternal obesity and other confounding variables. Overall it appears that birth weight is the most significant predictor of shoulder dystocia in the James Bay Cree, and in many other North American populations as well. Nonetheless, a large percentage of cases of shoulder dystocia do occur among infants weighing less than 4000 g. GDM appears to be a risk factor for shoulder dystocia due to its close relationship with infant macrosomia. The exact associations between GDM, birth weight and shoulder dystocia remains to be investigated further.

In addition to infant birth weight, elevated head and thoracic circumferences have also been noted in several studies as significant predictors of shoulder dystocia and birth trauma injury. We found that macrosomic Cree infants (≥ 4500 g) were longer, had larger head and thoracic circumferences and higher thoracic to head circumference ratios than non-macrosomic infants. Moreover, GDM offspring also had significantly higher thoracic to head circumference ratios compared with non-GDM offspring. Infants who had a birth trauma injury were also found to be longer and to have higher thoracic to head circumference ratios than non-injured infants. Previous studies by McFarland et al. (1998) and Modanlou et al. (1982) similarly found that macrosomic infants, particularly those of GDM pregnancies, have increased upper body fat deposition and high thoracic or shoulder to head circumference ratios relative to non-macrosomic infants. Other studies also report that increased thoracic circumferences and birth weight incurs increased risk of birth trauma injury and caesarean section delivery among offspring of GDM pregnancies (Langer et al. 1991).

It is possible therefore that the increased anthropometric measurements reported for macrosomic versus non-macrosomic Cree infants in this study provides a physical explanation for the propensity of macrosomic infant deliveries to incur shoulder dystocia events. It is also important to note that caesarean section delivery rates are lower for the James Bay Cree relative to other non-Native populations (Rodrigues et al. 2000); therefore higher prevalence rates of neonatal birth trauma injuries observed for James Bay Cree versus non-Native infants may be due in part to the higher number of vaginal deliveries of macrosomic infants with large thoracic to head circumference ratios (Rodrigues et al. 2000). Unfortunately, we cannot predict whether increasing the rate of caesarean section deliveries would actually help to reduce the occurrence of persistent birth injury for the Cree. In a US population study, Kolderup et al. (1997) found that a policy of elective caesarean section for macrosomia (≥ 4000 g) would necessitate 148 to 258 caesarean sections to prevent a single persistent injury. These authors support a trial of labour and judicious operative vaginal delivery for macrosomic infants. Conway and Langer (1998) recommend a three step strategy to help prevent birth injury in high risk population groups: improve glycemic control to reduce the rate of macrosomia; induce

of labour when a LGA fetus is suspected using ultrasound measurements; and suggest elective caesarean delivery of macrosomic fetuses to avoid vaginal delivery and thus shoulder dystocia. We suggest that prevention of shoulder dystocia and birth trauma injuries through reducing rates of infant macrosomia would be a beneficial goal for prenatal education programs in the James Bay Cree communities, given that strictly controlled maternal weight gain and glycemic control has been shown to result in smaller infant birth weights in non-Native populations (Snyder et al. 1994). Moreover, educational efforts to improve maternal weight weights prior to pregnancy will also be important in order to reduce the incidence of GDM in this population.

Given the research evidence presented herein concerning the elevated prevalence rates of birth trauma injury in the James Bay Cree population, the important question to answer for the Cree is "at what birth weight cut-off do we begin to see a significant increase in birth trauma injury?" If we consider 500 g increases in birth weight, we see a consistent graded increase in the rate of shoulder dystocia as birth weight increases. The rate of shoulder dystocia rose significantly from 0.6% in the < 4000 g category, to 7.1% among infants weighing 4500 to 4999 g, to 18.1% in infants weighing ≥ 5000 g. Clavicular fracture was also over two times higher among macrosomic Cree deliveries weighing over 5000 g (12.1%) as for those between 4500–5000 g (5.0%). A significant increase in the rate of caesarean section delivery was also observed for deliveries ≥ 4500 g compared with using the ≥ 4000 g cut-off to define macrosomia. For vaginal deliveries, the rate of $3^{rd}/4^{th}$ degree peritoneal tearing also increased most significantly for deliveries ≥ 5000 g (3.1% for deliveries < 4000 g to 12.5% for deliveries ≥ 5000 g). Overall we found that the most significant risk for birth trauma injury, and other macrosomia related complications in the Cree population occurred among infants weighing over 4500 g at birth, and that the risk increased even more significantly among infants weighing over 5000 g. In terms of medical care costs for macrosomic versus non-macrosomic infants, the prevalence caesarean section delivery and of infant hospital stays > 3 days were both significantly higher for infants weighing ≥ 4500 g versus those weighing < 4500 g.

We must acknowledge that our study did not assess the incidence of persistent birth injury complications beyond the neonatal period (e.g., at 3 to 6 months of life). This is an important drawback of this retrospective designed study, given that previous reports have indicated that most birth trauma fractures and brachial nerve palsies tend to resolve within the first 3 to 6 months of life (Kolderup et al. 1997, Lipscomb et al. 1995). Lipscomb et al. reviewed 157 spontaneous vaginal deliveries in infants weighing ≥ 4500 g and found a total of 7 palsies, and 8 fractures, all of which resolved by 2 months of age (1995). Kolderup et al. (1997) found that 1 in 200 infants in a US population sustained some form of birth trauma, whereas only 1 in 1000 of these infants had clinical complications still present at six months of age. In the James Bay Cree population, a higher rate of 8 out of 200 infants sustained some form of birth trauma injury, thus we could estimate that the incidence of long-term complications for Cree versus non-Native infants would also be higher. Obviously further prospective studies are warranted to investigate outcomes at 6 months and 1 year of life for Cree infants who experienced a birth trauma injury upon delivery. It will also be important to determine the extent to which tight maternal glycemic control and normalizations of prepregnancy weights and gestational weight gain can help to minimize the incidence of Cree births ≥ 4500 g and neonatal birth trauma injury.

Metabolic complications

In addition to high rates of birth trauma injury in the Cree population, prevalence rates of metabolic complications during the neonatal period were also elevated, particularly among offspring of GDM mothers. Overall prevalence rates of neonatal hypoglycemia, polycythemia, hyperbilirubinemia, and hypocalcemia were 8.8%, 1.7%, 28.7%, and 0.4% respectively. In comparison, other studies have reported somewhat lower rates for hypoglycemia and hyperbilirubinemia (5.1% and 16.5%), but higher rates for polycythemia, and hypocalcemia (13.3% and 5.5%) (Hod et al. 1991). Sermer et al. (1995) looked at non-diabetic mothers with varying degrees of glucose intolerance and did not find a significant association between maternal glucose intolerance and increased neonatal metabolic complications including hypoglycemia, and respiratory distress syndrome. Among James Bay Cree infants, the risk for hypoglycemia increased by a

factor of 2.7, for polycythemia by a factor of 2.4, and for hypocalcemia by a factor of 9.5 among GDM versus non-GDM offspring. In the Swampy Cree, Godwin et al. (1999) similarly found that GDM increased the risk for hypoglycemia by 7.3 times and for hypocalcemia by 8.9 times. These researchers also found that GDM increased the risk for neonatal jaundice requiring phototherapy treatment (RR=2.9; 95% CI 1.4-6.1) and for 5-minute Apgar score less than 7. Our findings do not support this association between GDM and phototherapy treatment, nor do they suggest that GDM is associated with lower 5-minute Apgar scores.

Another important point to emphasize in this comparative evaluation of prevalence rates of metabolic complications across different study populations is that different researchers use different cut-offs to define the same metabolic complications. For example, in our study we referred to hypoglycemia as infant blood glucose levels below 2.2 mmol/L whereas Hod et al. (1991) defined hypoglycemia differently as blood glucose levels less than 1.7 mmol/L for the first 72 hours or less than 2.2 mmol/L thereafter. Moreover, other studies have defined hypoglycemia based on whether or not an infant was treated with intravenous therapy to treat hypoglycemia (Sermer et al. 1995). If we had used one or more of these stricter definitions to define hypoglycemia in our study, then likely the prevalence rate would have been lower for the Cree. Similarly with defining hyperbilirubinemia, various studies in the literature have used cut-offs of ≥ 180 or ≥ 200 or ≥ 220 μmol, or conversely they have measured whether or not an infant was provided with phototherapy treatment for hyperbilirubinemia. In our study we used the cut-off of 180 μmol as well as considering whether or not the infant was given phototherapy treatment. Although hyperbilirubinemia was associated with macrosomia (≥ 4000 g), neither hyperbilirubinemia nor phototherapy treatment was significantly associated with maternal GDM status.

Another important methodological concern regarding neonatal assessment for metabolic complications in the Cree population is that according to hospital protocols, high-risk infants (e.g., macrosomic and GDM offspring) are supposed to be screened for hypoglycemia, polycythemia, and hypoglycemia during the first 24-72 hours of life

whereas low-risk infants are only screened if they show signs and symptoms of the conditions. Therefore consistent with our results, we expect to see a higher prevalence rate of hypoglycemia, polycythemia and hypocalcemia among macrosomic and GDM offspring simply because more of these infants were screened for the complications. If all infants had been routinely screened for these metabolic outcomes, then possibly the prevalence rate would have been even higher. As mentioned in the literature review, some studies have found an association between developmental delays and neonatal hypoglycemia; others have failed to confirm these findings. It would be interesting to conduct a longitudinal, prospective study to assess the developmental consequences (e.g., at 6 months, 1 year, 3 years, 5 years) associated with neonatal hypoglycemia. According to the research evidence, we would expect to see developmental delays among untreated, but not treated, infants who experienced neonatal hypoglycemia. In the Cree population, where most infants are treated for hypoglycemia within the first 24-48 hours of life, the extent of long-term developmental damage associated with hypoglycemia should be minimal.

Prevalence and predictors of macrosomia and GDM

The overall prevalence of macrosomia in this study, defined alternately as birth weight ≥ 4000 g and birth weight ≥ 4500 g, was 36.1% and 10.4% respectively, which is comparable to rates reported earlier in the literature by Armstrong et al. (1998) and Rodrigues et al. (2000) for the Cree population. We found that the prevalence of macrosomic infants (≥ 4500 g) delivered by non-GDM Cree mothers was 8.4%. This rate is considerably higher than the 1-2% reported for the general population (Spellacy et al. 1985). In contrast, the prevalence of macrosomic infants (≥ 4500 g) delivered by Cree mothers with GDM was 20%. This rate is not significantly different from the rates of 13-19% reported for other non-Native populations of mothers with GDM (Bérard et al. 1998, Gregory et al. 1998). These findings suggest that the James Bay Cree have prevalence rates of macrosomia that are higher than those of other populations for reasons independent of maternal GDM status. Maternal obesity and other genetic/lifestyle factors, in addition to GDM, are inevitably driving the high rates of macrosomia in the Cree population.

The prevalence of GDM estimated for the James Bay Cree was 16.6% (95% CI 14.6-18.6%). This rate is slightly higher (but within the 95% CIs) than the rate of 12.8% reported earlier by Rodrigues et al. (1999a) (95% CI 10.1-15.5%). Predictors of GDM among Native women have been identified previously in numerous studies (Harris et al. 1997, Caulfield et al. 1998, Rodrigues et al. 1999b). Overall, the most significant predictors of GDM identified for the James Bay Cree were pregravid obesity and maternal age ≥ 30 years. Rodrigues et al. similarly identified that maternal age and pregravid weight were independent predictors of GDM among James Bay Cree women (1999b). A recent study by Godwin et al. (1999) also found that maternal age, diastolic blood pressure of 80 mm Hg or higher at the first prenatal visit, weight greater than 80 kg at the first prenatal visit, and having a first-degree relative with diabetes were independent predictors of GDM among Swampy Cree women in Ontario.

Implications of these research findings for clinical practice

This research investigation provides valuable new information about the neonatal health of James Bay Cree infants. Most health care professionals who work with the James Bay Cree are surely aware of the high average birth weight of Cree infants, and high prevalence rates of GDM and infant macrosomia. However, most practitioners would likely speculate that there are minimal short and long-term ramifications associated with GDM and macrosomia for Cree infants. Although the overall rate of birth trauma injuries in the Cree population is small (4.3%), this rate is considerably higher than rates reported previously for other non-Native populations in North America (Wikstrom et al. 1988, Kolderup et al. 1997). The overall prevalence rate of neonatal hypoglycemia is also high among James Bay Cree infants relative to other population groups (Hod et al. 1991). Therefore, our research findings indicate that there *is* a high rate of neonatal morbidity in the James Bay Cree population, and that the increased neonatal morbidity is significantly associated with the high rates of GDM and macrosomia (≥ 4500). On the other hand, we have identified very low prevalence rates of LBW for the Cree population relative to other non-Native populations in Canada (Luginaah et al. 1999).

Prevention of infant macrosomia through encouraging tight maternal glycaemic control during pregnancy via diet, exercise and insulin therapy may be an important key to reducing the incidence of neonatal birth trauma injuries and metabolic complications. Moreover, preventing infant macrosomia may have the additional long-term benefits of reducing the occurrence of obesity and type 2 diabetes in subsequent generations (Seidman et al. 1998, Lucas et al. 1999). Recent pilot studies have demonstrated the limitations and feasibility of implementing exercise programs and prenatal dietary counselling to help improve GDM pregnancy outcomes for Native Canadian women and infants (Dyck et al. 1999, Gray-Donald et al. 2000). A special working group of the James Bay Cree Regional Child and Family Services Committee (2000) recently recommended that intervention efforts to reduce weight gain in pregnancy and GDM in Cree communities should incorporate group education sessions that encourage local support networks, involve elder women and local midwives from the communities, offer dietary counselling, and encourage the promotion of physical activities that appeal to girls and women. They also recommend that nutritional advice for Cree women should also be individualized to take into account the patient's cultural practices, pregravid weight, weight gain, and usual physical activity patterns, and should be modified as needed throughout pregnancy to achieve glycemic goals. A relatively small gain of approximately 6 kg is recommended for patients who are obese (BMI $\geq$ 30 kg/m^2) when they become pregnant, and a proportionately greater weight gain (up to 18 kg) is recommended for patients who are underweight (BMI $\leq$ 20 kg/m^2) at the onset of pregnancy (Metzger et al. 1998).

Future studies are certainly needed to ascertain the specific degree of "tight" glycemic control that is necessary to reduce the overall risk of neonatal morbidity for the Cree population through improving diet and exercise patterns. Further studies should also investigate the accuracy of using fetal ultrasound measurements (e.g., fetal weight, chest and head circumference) to assess the risk of birth trauma injury for vaginal deliveries of macrosomic infants. We suggest that maternal education programs aimed at reducing the incidence of GDM and pregravid obesity in the Cree communities, combined with the improved awareness of physicians concerning the utility of ultrasound to predict fetal

weight and outcome, could help to reduce the overall incidence of birth injury and metabolic complications in the James Bay Cree population, hopefully without causing a significant increase in the rate of caesarean section deliveries.

CONCLUSIONS

We have identified that in the short term, GDM and infant macrosomia are associated with increased neonatal morbidity for the Cree. Specifically, macrosomia (≥ 4500 g) is associated with an increased incidence of shoulder dystocia, clavicular fracture, neonatal hypoglycemia, caesarean section delivery, and infant hospital stay greater than 3 days, and GDM is associated with an increased incidence of hypoglycemia, polycythemia, and hypocalcemia among the Cree. Godwin et al. (1999) similarly found that GDM is associated with an increase in adverse pregnancy outcomes for the Ojibwa-Cree population of northern Ontario. Moreover, there are numerous non-Native population studies populations that have demonstrated associations between GDM, macrosomia and increased maternal and neonatal morbidity. At this time we cannot ascertain whether or not the higher rate of birth injury observed in the Cree population relative to other non-Native North American populations is related to their low overall rate of caesarean section delivery, nor if the birth injuries and metabolic complications reported for Cree infants tend to persist beyond the neonatal period. There is limited evidence in the literature to support that increasing the rate of caesarean section delivery would truly help to reduce the overall incidence of persistent birth injury in other populations. There is some research evidence from pilot studies in Native Canadian communities in Saskatchewan and in the James Bay Cree region to suggest that culturally appropriate diet and exercise intervention programs may be useful to improve pregnancy outcomes for Native mothers with GDM. Future studies to investigate the effectiveness of strict glycemic management on improving neonatal outcomes, and to investigate the growth patterns of macrosomic infants, as well as the long-term physical and developmental consequences associated with birth trauma injuries and metabolic complications, beyond the neonatal period are warranted for the James Bay Cree population.

Figure 1. Flow chart: included versus excluded subjects

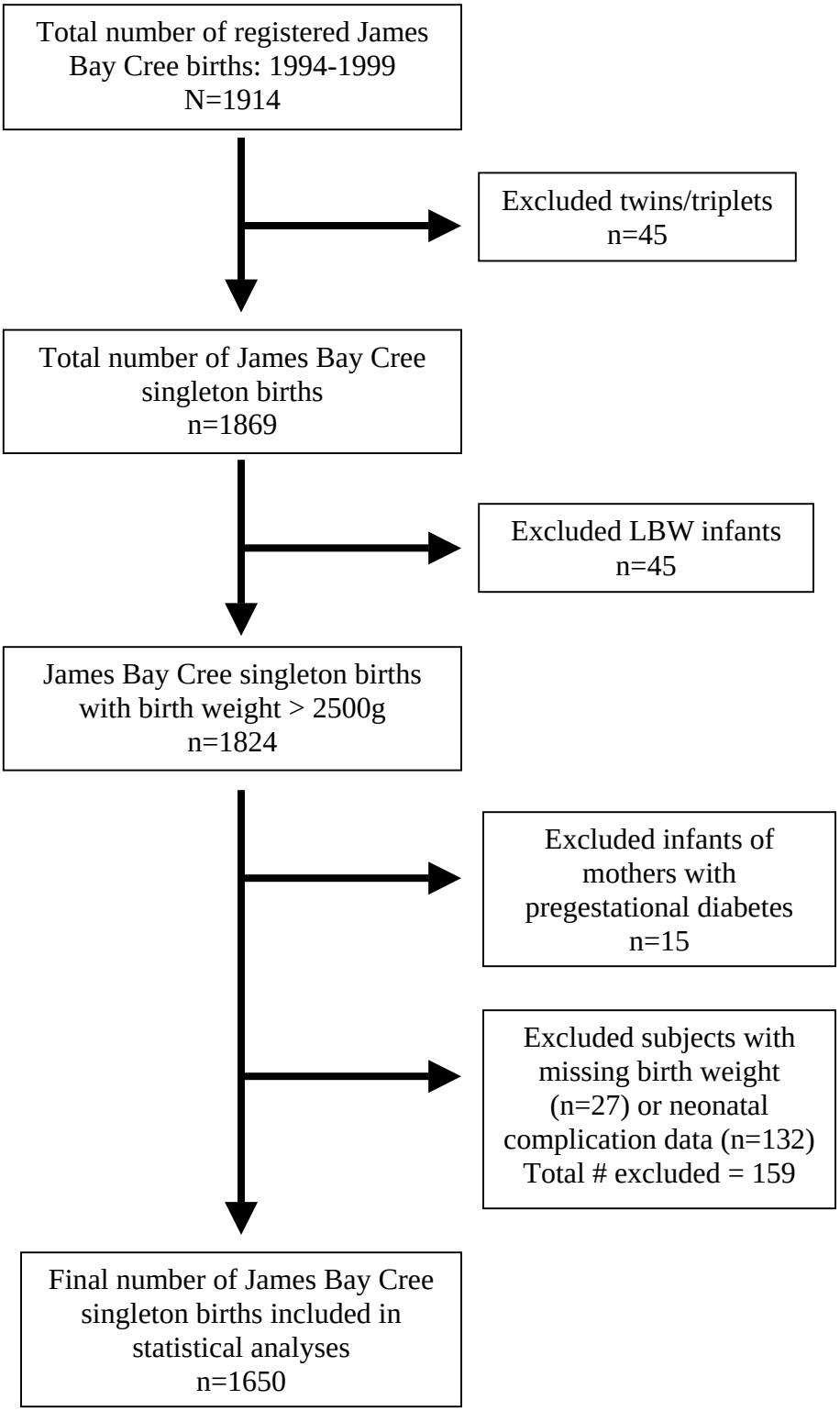


Figure 2. Birth weight distribution of included Cree subjects (n=1650)

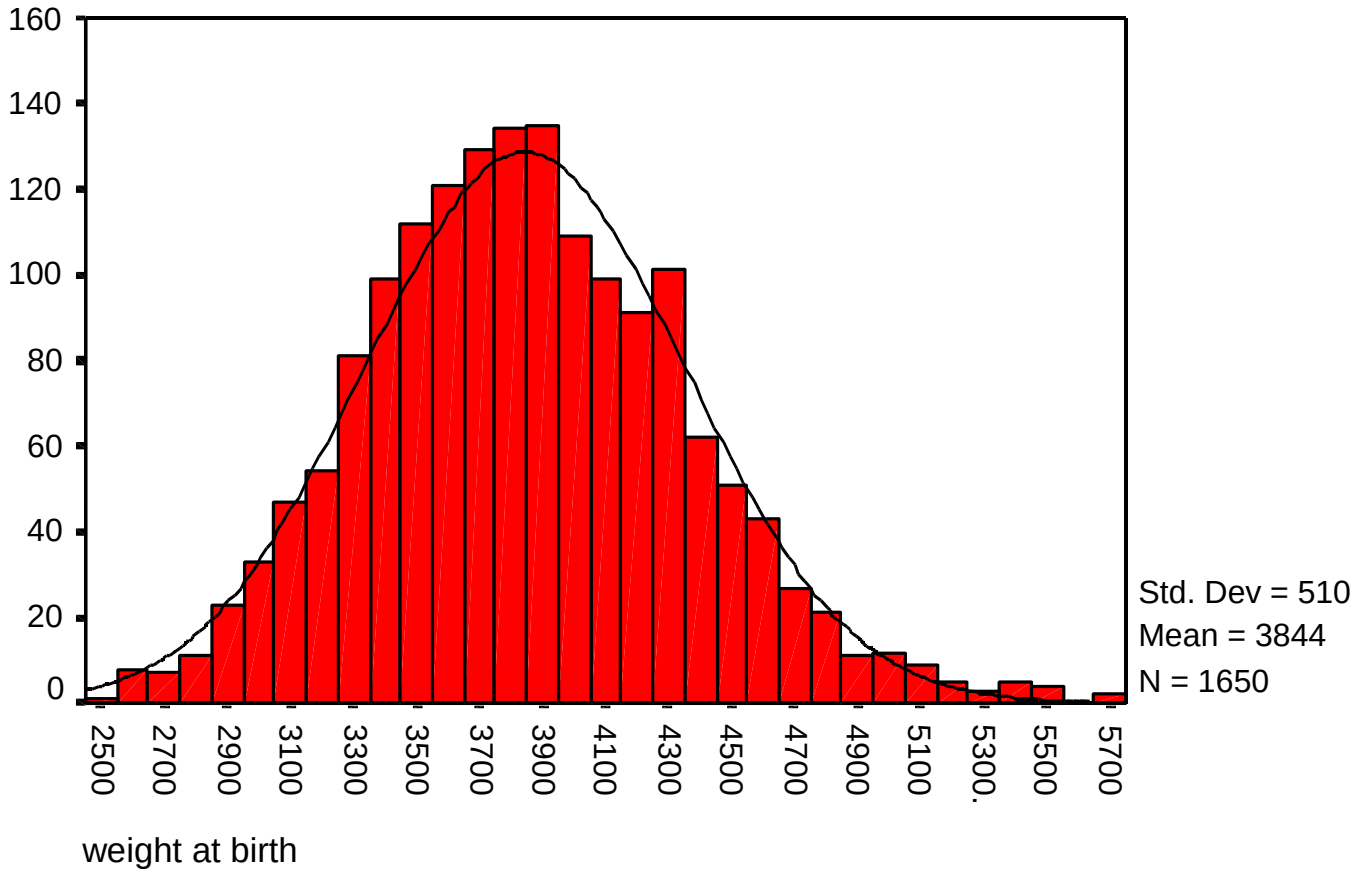
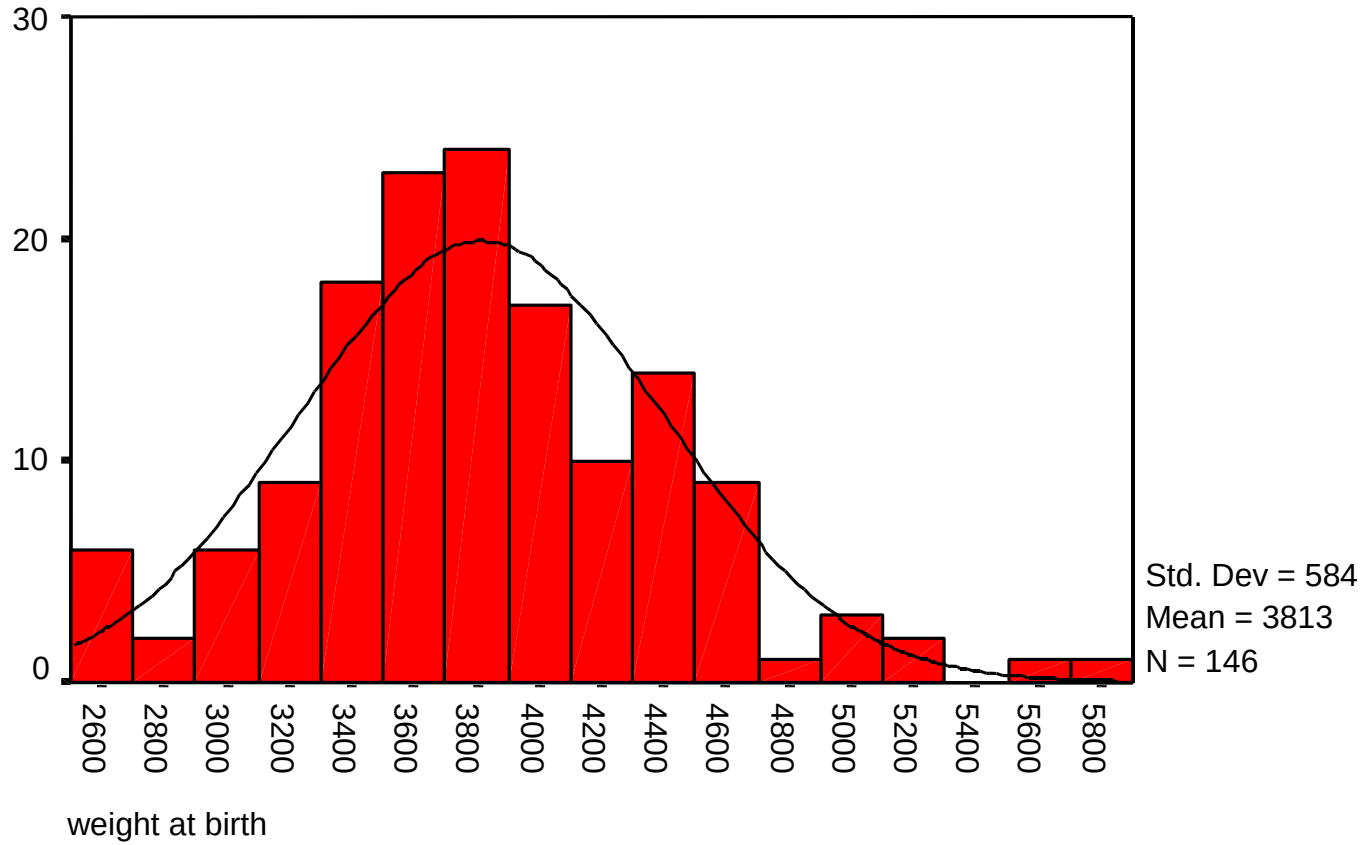


Figure 3. Birth weight distribution of excluded Cree infants (n=132)[1,2]



[1] Only 132 out of the 159 excluded subjects had birth weight information
[2] Twins, LBW, and pre-diabetic offspring subjects not reported as "excluded"

Table 1. Cree infant births weight distribution (included versus excluded subjects)

Birth weight	Included subjects n=1650	Excluded subjects [1] n=132 [2]
2500-2999 g	63 (3.8 %)	6 (4.5%)
3000-3499 g	363 (22.0 %)	32 (24.2%)
3500-3999 g	629 (38.1 %)	50 (37.9%)
4000-4499 g	423 (25.6 %)	28 (21.3%)
4500 4999 g	140 (8.5 %)	11 (8.3%)
≥ 5000 g	32 (1.9 %)	5 (3.8%)

[1] Excluded refers to subjects with missing birth complication information
[2] 159 - 27 subjects missing birth weight information = 132 excluded subjects with birth weight information

Table 2. Infant and maternal characteristics of Cree deliveries (included versus excluded subjects)

	Included subjects N=1650		Excluded subjects N=159		p-value
	n		n		
Birth weight (g)	1650	3844 ± 511	132	3813 ± 584	0.54
Gestational age (wks)	1650	39.2 ± 1.3	133	38.9 ± 1.5	0.012
Maternal age (yrs)	1650	24.0 ± 5.6	144	23.6 ± 5.4	0.32
Parity	1623	1.6 ± 1.5	114	1.4 ± 1.3	0.31
Pregravid weight (kg)	969	80.7 ± 17.3	23	78.3 ± 25.4	0.42

[1] Excluded refers to subjects with missing birth complication information and/or birth weight information

Table 3. Method of delivery of Cree infants based on birth weight categories

Birth Weight	Vaginal Delivery			Caesarean Section Delivery
	Unassisted	Forceps	Vacuum	
	n (%)	n (%)	n (%)	n (%)
2500-3999 g	842 (79.8%)	38 (3.6%)	27 (2.6%)	148 (14.0%)
4000-4499 g	315 (74.1%)	23 (5.4%) [1]	23 (5.4%) [1]	65 (15.3%)
≥ 4500 g	115 (68.0%)	9 (5.3%) [1]	8 (4.7%) [1]	37 (21.9%) [2]
ALL DELIVERIES	1262 (77.3%)	68 (4.2%)	58 (3.6%)	245 (15.0%)

[1] Significantly higher rate of forceps/vacuum assisted vaginal delivery for infants weighing 4000-4499 g and ≥ 4500 g compared with infants weighing 2500–3999 g using chi-square tests ($p < 0.01$)

[2] Significantly higher caesarean section rate for infants weighing ≥ 4500 g compared with other birth weight categories < 4500 g using chi-square tests ($p < 0.05$)

Table 4. Carbohydrate tolerance (GDM versus IGT versus high screen no OGTT) of Cree mothers

GDM status	Number of subjects (N=1650) [1]
Normal	910 (66.0%)
GDM	190 (13.8%) [2]
IGT	123 (8.9%)
High screen no OGTT	156 (11.3 %)

[1] 271 mothers charts lacked GDM status information (1379 + 271 = 1650)
[2] Using the positive predictive value (PPV) of: [26% (x 156 high screen no OGTT) + 910] / 1650, the estimated prevalence of GDM was 16.6%

Table 5. Infant and maternal characteristics of macrosomic versus non-macrosomic Cree births (macrosomia defined alternatively as birth weight ≥ 4000 g and birth weight ≥ 4500 g)

	Non-macrosomic BW < 4000 g (n=1054)	Macrosomic BW ≥ 4000 g (n=595)	p-value (one-sided)	Non-macrosomic BW < 4500 g (n=1477)	Macrosomic BW ≥ 4500 g (n=172)	p-value (one-sided)
Birth weight (g)	3540 ± 311	4382 ± 316	<0.001	3834 ± 410	4785 ± 269	<0.001
Birth length (cm)	51.1 ± 2.0	53.6 ± 1.9	<0.001	51.7 ± 2.1	54.6 ± 1.9	<0.001
Head circumference (cm)	35.3 ± 1.2	36.8 ± 1.3	<0.001	35.6 ± 1.3	37.4 ± 1.5	<0.001
Thoracic circumference (cm)	34.4 ± 1.5	36.8 ± 1.3	<0.001	34.9 ± 1.7	38.1 ± 1.5	<0.001
Thoracic to head circumference ratio	0.98 ± 0.04	1.00 ± 0.04	<0.001	0.98 ± 0.04	1.02 ± 0.04	<0.001
Gestational age (wks)	39.0 ± 1.4	39.7 ± 1.1	<0.001	39.2 ± 1.3	39.8 ± 1.1	<0.001
Mother's age (yrs)	23.8 ± 5.7	24.3 ± 5.5	0.05	24.0 ± 5.7	24.4 ± 5.0	0.16
Parity	1.5 ± 1.5	1.6 ± 1.5	0.04	1.5 ± 1.5	1.80 ± 1.65	0.13
Pregravid weight (kg)	78.7 ± 17.4	84.7 ± 16.4	<0.001	79.9 ± 17.2	79.9 ± 16.8	<0.001
Height (cm)	162.5 ± 6.1	163.3 ± 5.5	0.14	162.6 ± 5.9	164.1 ± 5.7	0.10

Table 6. Multivariable predictors of infant macrosomia (≥ 4500 g) among Cree women

Characteristic	p-value	Adjusted OR (95% CI) [1]
Maternal age (≥ 35 years)	0.11	3.42 (0.80-14.60)
Multiparity (≥ 2)	0.58	0.88 (0.56-1.38)
Pregravid obesity (> 77 kg)	< 0.01	0.41 (0.25-0.68)
Gestational diabetes	< 0.01	2.80 (1.63-4.81)

[1] Results derived using multiple logistic regression analysis

Table 7. Maternal GDM status of Cree infants compared across birth weight categories [1,2]

	Birth weight < 4000 g n=885	Birth weight 4000-4499 g n=355	Birth weight ≥ 4500 g n=139
	n (%)	n (%)	n (%)
Normal glucose tolerance	615 (69.5)	219 (61.7)	76 (54.7)
GDM	90 (10.2)	62 (17.5)	38 (27.3)
IGT	85 (9.6)	29 (8.2)	9 (6.5)
High screen no OGTT	95 (10.7)	45 (12.7)	16 (11.5)

[1] The total number of subjects with GDM information reported in this table is n=1379 (271 cases out of 1650 were missing GDM information)
[2] A significant increase was noted in the prevalence of GDM across birth weight categories (chi-square test used); $p < 0.001$

Table 8. Characteristics of infants who experienced more than one birth trauma event (n=7)

Birth weight (g)	Shoulder dystocia	Other injury	Metabolic complications	Maternal GDM	Oxygen administered post-delivery	Apgar Score (1min, 5 min, 10 min)	Infant sex
4870	Yes	Clavicular fracture	Hyperbilirubinemia, hypoglycemia	No	Yes	4,8,9	Female
4350	Yes	Brachial plexus injury	None	Yes	Yes	1,6,9	Female
5130	Yes	Clavicular fracture	None	No	Yes	7,9,10	Male
4405	Yes	Clavicular fracture	Hyperbilirubinemia	Yes	No	6,8,10	Female
5195	Yes	Brachial plexus injury	Hyperbilirubinemia, hypoglycemia	Yes	Yes	5,9,10	Male
3805	Yes	Clavicular fracture	None	Yes	No	8,9,9	Female
5330	Yes	Clavicular fracture, brachial plexus injury, Erb's palsy	Hyperbilirubinemia	Yes	Yes	3,8,10	Female

Table 9. Prevalence of birth trauma injuries among Cree deliveries compared across birth weight categories

	All James Bay Cree births n=1650	Birth weight < 4000 g n=1055	Birth weight 4000-4499 g n=423	Birth weight ≥ 4500 g n=172
Overall birth trauma injury	67 (4.1%)	14 (1.3%)	24 (5.7%)	29 (16.9%)
Shoulder dystocia	42 (2.5%)	6 (0.6%)	20 (4.7%)	16 (9.3%)
Clavicular fracture	15 (0.9%)	3 (0.3%)	2 (0.5%)	10 (5.8%)
Brachial plexus injury	4 (0.2%)	1 (0.1%)	1 (0.2%)	2 (1.2%)
Erb's Palsy	2 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.6%)
Humerus fracture	2 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Facial paralysis	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Calf paralysis	1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

Table 10. Delivery outcomes for macrosomic versus non-macrosomic Cree infants

Outcome	No. (and %) of pregnancies		OR (and 95% CI) [2,3]
	With macrosomia [1]	Without macrosomia	
Caesarean section delivery	36 (21.4)	208 (14.1)	1.62 (1.09-2.40)
Overall birth trauma injury	29 (16.9)	38 (2.6)	8.60 (3.85-19.19)
Shoulder dystocia	16 (9.3)	26 (1.8)	6.75 (2.83-16.09)
Clavicular fracture	10 (5.8)	5 (0.3)	18.18 (6.14-53.82)
Brachial plexus injury	2 (1.2)	2 (0.1)	8.68 (1.22-62.01)
Erb's Palsy	1 (0.6)	1 (0.07)	Non-significant
Hypoglycemia	38 (22.1)	106 (7.2)	3.30 (2.17-5.01)
Hyperbilirubinemia	59 (34.3)	412 (28.0)	Non-significant
Hospital stay > 3 days	73 (44.8)	423 (30.2)	1.57 (1.004-2.448)
Five minute Apgar score < 7	1 (0.6)	16 (1.1)	Non-significant

[1] Macrosomia defined as birth weight ≥ 4500 g
[2] Multiple logistic regression analyses adjusted for GDM, obesity, maternal age, parity, gestational age
[3] Non-significant refers to $p > 0.05$

Table 11. Delivery outcomes for women with and without GDM

Outcome	No. (and %) of pregnancies		OR (and 95% CI) [1,2]
	With GDM	Without GDM	
Overall birth trauma injury	9 (4.7)	43 (2.9)	Non-significant
Shoulder dystocia	6 (3.2)	36 (2.5)	Non-significant
Clavicular fracture	5 (2.6)	10 (0.7)	4.81 (1.70-13.66)
Brachial plexus injury	0 (0.0)	4 (0.3)	Non-significant
Hyperbilirubinemia	60 (31.9)	411 (28.3)	Non-significant
Hypoglycemia	34 (18.1)	110 (7.6)	2.77 (1.85-4.17)
Polycythemia	7 (3.7)	21 (1.4)	2.91 (1.26-6.69)
Hypocalcemia	3 (1.6)	4 (0.3)	5.35 (1.19-24.08)
Oxygen therapy	58 (30.9)	359 (24.7)	1.45 (1.06-2.00)
Hospital stay > 3 days	79 (43.2)	417 (30.2)	1.88 (1.38-2.54)
Five minute Apgar score < 7	4 (2.1)	13 (0.9)	Non-significant

[1] Multiple logistic regression analyses adjusted for obesity, maternal age, parity, gestational age
[2] Non-significant refers to $p > 0.05$

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