EPIDEMIOLOGY OF GESTATIONAL DIABETES MELLITUS AND INFANT MACROSOMIA AMONG THE CREE OF JAMES BAY

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PREFACE

In this thesis, prevalence and risk factors of gestational diabetes mellitus (GDM) and infant macrosomia were examined among the Cree of James Bay, and the risk for these outcomes was compared with non-Native Canadian women. Chapter 1 provides the rationale for the study and enlists specific objectives of this doctoral research. An in-depth literature review on GDM and infant macrosomia is presented in Chapter 2. The findings of this research are presented in the form of three manuscripts in Chapters 3-5. Chapter 3 investigates the prevalence of GDM among the Cree using standardized criteria. Chapter 4 examines reasons for the high prevalence of GDM among the Cree and compares the risk for GDM between Cree women and Canadian non-Native women. Chapter 5 documents independent risk factors for infant macrosomia among the Cree and compares these with risk factors among non-Native Canadians. The thesis ends (chapter 6) with a summary of the findings and an overall conclusion.

ABSTRACT

The objectives of this research were to determine the prevalence of gestational diabetes mellitus (GDM) among the Cree of James Bay, identify independent risk factors for GDM and infant macrosomia in this population and compare the risk for GDM and infant macrosomia among Cree women with Canadian non-Native women. The prevalence of GDM using the National Diabetes Data Group criteria among the Cree was 12.8% (95% CI: 10.1-15.5), among the highest ever reported for an Aboriginal group. Independent risk factors for GDM among the Cree were advanced age, pregravid overweight and previous GDM. A comparison of risk of GDM between Cree and non-Native women revealed a significant interaction between ethnicity and pregravid weight. Overweight Cree women were at an elevated risk for GDM compared with overweight non-Native women (OR: 2.3, 95% CI: 1.3-3.8), whereas the risk for GDM was not statistically different between normal weight Cree and non-Native women (OR: 1.4, 95% CI: 0.7-2.7) after adjusting for age, parity, and smoking status. Mean birth weight among Cree infants was 3859 ± 519 g, the highest reported for any ethnic group in the world. Macrosomia prevalence was also high at 34.3%. Independent risk factors for macrosomia among the Cree were advanced age, pregravid overweight and GDM. A significant interaction was noted between ethnicity and GDM on risk for macrosomia. GDM increased the risk for macrosomia 4.5-fold among the Cree but had no significant effect among non-Natives. After adjusting for age, parity, pregravid weight, gestational weight gain, GDM, gestational duration and smoking status, Cree infants remained heavier than non-Native infants by 235 g. The results of this research indicate the need to control pregravid obesity through culturally acceptable dietary modifications and exercise in order to minimize the risk for GDM among Cree women. The significant impact of GDM on risk for macrosomia among the Cree calls for the re-evaluation of the existing treatment strategies for GDM.

RÉSUMÉ

Les objectifs de cette recherche étaient de déterminer la prévalence de diabète mellitus gestationnel (DMG) chez les Cree de la Baie James, d'identifier des facteurs de risque indépendants pour le DMG et pour la macrosomie infantile dans cette population, et de comparer le risque pour le DMG et la macrosomie infantile chez les femmes Cree avec celui de femmes canadiennes non-autochtones. La prévalence de DMG chez les Cree était 12.8% (95% IC: 10.1-15.5) d'après le "National Diabetes Data Group", un des plus élevé jamais rapporté pour un groupe autochtone. Les facteurs de risque indépendants pour le DMG chez les Cree étaient un age avancé, un surplus de poids pré-gravide et du DMG antérieur. Une comparaison du risque pour le DMG entre les Cree et les femmes non-autochtones a révélé une interaction significative entre l'ethnie et le poids pré-gravide. Les femmes Cree avec un surplus de poids courraient un risque élevé pour le DMG comparativement aux femmes non-autochtones avec un surplus de poids (OR: 2.3, 95% IC: 1.3-3.8), tandis que le risque pour le DMG n'était pas statistiquement différent entre les femmes Cree et les femmes non-autochtones de poids normal (OR: 1.4, 95% IC: 0.7-2.7) après ajustement pour l'âge, la parité, et le statut de fumeur. Le poids moyen à la naissance des nouveau-nés Cree était 3859 ± 519 g, le plus élevé de tous les groupes ethniques au monde. La prévalence de la macrosomie était aussi élevée à 34.3%. Les facteurs de risque indépendants pour la macrosomie chez les Cree étaient l'âge avancé, le poids pré-gravide, et le DMG. Une interaction significative a été noté entre l'ethnie et le DMG pour le risque de macrosomie. Chez les Cree, le risque de macrosomie est 4.5 fois plus élevé s'il y a présence de DMG, mais cet effet n'est pas observé chez les non-autochtones. Les résultats de la présente étude indique le besoin de contrôler l'obésité pré-gravide par des modifications nutritionnelles qui seraient culturellement acceptables et des exercices, dans le but de minimiser le risque de DMG chez les femmes Cree. L'impact significatif du DMG sur le risque de macrosomie chez les Cree demande une réévaluation des stratégies en place pour le DMG.

THESIS GUIDELINES

This thesis uses a manuscript–based format by including three papers as published or submitted for publication. As per Faculty regulations, the following five paragraphs are reproduced from the Guidelines for Thesis Preparation by the Faculty of Graduate Studies and Research.

> ***"Candidates have the option of including, as part of the thesis, the text of a paper(s) submitted or to be submitted for publication, or the clearly-duplicated text of a published paper(s). These texts must be bound as an integral part of the thesis.***
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> ***In the case of the manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the***

examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers. Under no circumstances can a co-author of any component of such a thesis serve as an examiner for that thesis."

ORIGINAL CONTRIBUTIONS

This doctoral research is original both with regard to the objectives proposed and the findings obtained. The candidate was responsible for the conception and design of the studies, part of the data collection, solely responsible for data management and analyses and the preparation of the manuscripts. Dr. K. Gray-Donald, the thesis supervisor, worked with the candidate in the formulation of research questions and study design, provided guidance in interpreting the data and reviewed the manuscripts. Dr. E. J. Robinson reviewed all three manuscripts and ensured approval of the manuscripts by the Cree health board before submission of these to peer-reviewed journals. Dr. H. Ghezzo provided statistical guidance for the second manuscript (chapter 4). Dr. M. S. Kramer reviewed the last manuscript (chapter 5) and provided insightful comments.

This is the first study to document GDM prevalence among the Cree of James Bay using standardized criteria. The prevalence of GDM of 12.8% among the James Bay Cree (chapter 3) is the second highest prevalence reported for an aboriginal group worldwide. This prevalence estimate is more accurate than those reported for other Native populations because it includes an estimate of GDM cases among those with high screen values who did not undergo a diagnostic test, which has not been done previously.

Very little information is available on independent risk factors for GDM in Aboriginal populations. Further, none of these studies determined the effect of prediagnostic rate of weight gain, diet and physical activity on GDM risk. Our study is the first to explore the effects of these risk factors in well-controlled analyses and provides important new information on the independent or interactive effects of risk factors for GDM in an Aboriginal group.

Cree infants have the highest reported mean birth weight in the world and a high prevalence of infant macrosomia. Yet risk factors for macrosomia in this population have not been previously documented. This is the first well-controlled study which identified independent risk factors for infant macrosomia in this Aboriginal population.

No study among Aboriginal people has used non-Native controls to explore ethnic differences in risk for GDM or infant macrosomia. This research was the first to compare the risk for GDM and infant macrosomia between a Canadian Native group and non-

Native Canadian women after rigorously controlling for differences in the distributions of risk factors between the two populations. Population differences in these risk factors are very important in terms of body weight and age at delivery.

This study is the first to report an interaction between body weight and ethnicity as a determinant of GDM (chapter 4). Only obese Cree women were at an increased risk for GDM compared with obese non-Native women. This finding is very important because it indicates that maintaining a normal body weight protects against GDM among the Cree and emphasizes the need to target pregravid obesity among Cree women using culturally acceptable interventions.

Another interesting interaction with important implications is that of GDM with ethnicity as a risk factor for infant macrosomia (chapter 5). GDM was associated with increased risk for infant macrosomia among the Cree but had no effect among non-Native infants after controlling for age, parity, pregravid weight, gestational weight gain and smoking status. The differential effect of GDM on infant macrosomia in the two populations points to differences in treatment modalities for GDM and underscores the need to re-examine treatment strategies for GDM among the Cree.

In summary this thesis has made significant contributions to the existing Aboriginal diabetes and pediatric literature by documenting the epidemiology of gestational diabetes mellitus (GDM) and infant macrosomia in a Canadian Native group and determining ethnic differences in these outcomes in well-controlled analyses.

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CHAPTER 1
INTRODUCTION

Maternal health status during pregnancy and infant birth weight are important determinants of perinatal health. In particular, gestational diabetes mellitus (GDM) and infant macrosomia are two important perinatal health concerns among North American Native peoples which will be the focus of this doctoral research.

Infant size at birth is used as an indicator of fetal growth and is a critical determinant of perinatal morbidity and mortality (Institute of Medicine 1990). The risk of infant mortality increases with both low (<2500 g) and high (>4000 g) birth weight (Hogue et al 1987). Risk factors for low birth weight have been extensively researched (Kramer 1987), whereas few studies have investigated independent determinants of excessive fetal growth (macrosomia). This is important because infant macrosomia not only increases the risk for infant mortality but also the risk for operative deliveries and birth trauma associated with asphyxia, meconium aspiration, shoulder dystocia, brachial plexus injury and clavicular fractures (Modanlou et al 1980, Stevenson et al 1982, Boyd et al 1983, Spellacy et al 1985, Lazer et al 1986, Wilkstrom et al 1988, Kolderup et al 1997). Long-term consequences of infant macrosomia are uncertain, however, with some studies reporting subsequent obesity among macrosomic infants (Berkey et al 1998) and others refuting the finding (Hulman et al 1998, Seidman et al 1998).

GDM is associated with an increased risk of various short- and long-term adverse outcomes. Short-term pregnancy complications associated with GDM include increased risk of macrosomia, operative deliveries, birth trauma, infant hypoglycemia, polycythemia and hyperbilirubinemia (Hod et al 1991, Rey et al 1996, Adams et al 1998). In the long-term, somewhere between 20-80% of women with GDM may develop Type 2 diabetes (Damm et al 1992, Kaufmann et al 1995, Kjos et al 1995, Peters et al 1996, Simmons 1996) and their offspring exposed to a diabetic environment in-utero are also at an increased risk for subsequent obesity and diabetes (Silverman et al 1991, Pettitt et al 1993) and impairment in psychomotor development (Rizzo et al 1995).

A detailed review of determinants of GDM and infant macrosomia in the general population can be found in chapter 2. In brief, risk factors for GDM in the general

population are advanced age, multiparity, non-White ethnicity, pregravid obesity, weight gain in early adulthood, smoking and physical inactivity during pregnancy (Dooley et al 1991, Berkowitz et al 1992, Dornhorst et al 1992, Solomon et al 1997). Determinants of infant macrosomia in the general population include advanced maternal age, tall stature, multiparity, pregravid obesity, excessive gestational weight gain, maternal diabetes, male infant gender and post-term delivery (ACOG 1992). A review of the literature on risk factors for these outcomes points to several issues that warrant further investigation:
a) Few well-controlled studies have explored independent or interactive effects of risk factors for GDM or infant macrosomia; b) The effects of rate of gestational weight gain and diet before GDM diagnosis on GDM risk have not been elucidated; c) Ethnic differences in GDM prevalence (Dooley et al 1991, Berkowitz et al 1992, Dornhorst et al 1992) and mean birth weight (Meredith et al 1970, Cogswell and Yip 1995, Wen et al 1995) have been reported, but whether these differences are attributable to genetic differences or differences in environmental influences between populations remains uncertain.

The perinatal health status of Canadian First Nations or Native peoples is reportedly poor compared with the general Canadian population (MacMillan et al 1996, Tookenay 1996). Although infant mortality rates are on the decline among Canadian Native peoples, infant mortality rates remain almost twice as high (13.8/1000 live births vs. 7.3/1000 live births) and postneonatal mortality rates are almost four times higher than the general Canadian population (MacMillan et al 1996). However, low birth weight rates (which might normally explain poorer outcomes) are not elevated among Canadian Natives peoples (2.5-5.8%) (Munroe et al 1984, Thomson 1990, Armstrong et al 1998) compared with the general Canadian population (5.9%) (Joseph and Kramer 1997). GDM (Sugarman 1989, Livingston et al 1993, Murphy et al 1993, Rith-Najarian et al 1996, Benjamin et al 1993, Harris et al 1997) and infant macrosomia (Thomson 1990, Murphy et al 1993, Dyck and Tan 1995, Caulfield et al 1998) are increasingly important perinatal complications reported among some Native peoples in North America. However, accurate estimates of the prevalence of these outcomes and their determinants among different Native groups, especially in Canada, are particularly lacking. The Cree of James Bay (northern Quebec) have a high prevalence of Type 2 diabetes, being twice as high

among Cree women as among men (Brassard et al 1993). They also have the highest reported mean birth weight for an ethnic group world-wide (Armstrong et al 1998). The prevalence of GDM among Cree women has not been documented, nor have independent determinants of GDM and infant macrosomia in this population been previously identified. Also, no studies to date among Aboriginal people have used a comparative group of non-Native women from the general population to determine if Aboriginal women are more susceptible to GDM and infant macrosomia, once population differences in distributions of risk factors are controlled.

The primary objectives of this doctoral research were therefore to address these lacunae in the area of perinatal health of Aboriginal people and advance our understanding of ethnic differences in these perinatal outcomes.

1.1 Research Objectives

1) To establish the prevalence of Gestational Diabetes Mellitus (GDM) among the Cree of James Bay using standardized criteria.
2) To identify and quantify the effects of independent determinants of GDM and infant macrosomia among the Cree.

   In particular, the effects of age, parity, previous GDM, pregravid body weight, height, smoking status, prediagnostic rate of weight gain, diet and physical activity patterns were evaluated to determine risk for GDM.

   The risk imparted by the following variables for infant macrosomia was also determined: age, parity, pregravid body weight, height, gestational weight gain, smoking status, diet and physical activity patterns.
3) To determine if Cree women are at an elevated risk for GDM and infant macrosomia compared with non-Native women, after controlling for differences in the distributions of risk factors for these outcomes.

   Specifically, the effect of ethnicity (Cree vs. non-Native) on GDM was determined by using two approaches: a) statistically adjusting for differences in age, parity, pregravid weight or body mass index, height and smoking status

   b) frequency matching Cree women with non-Native women for age and body weight.

Similarly, the effect of ethnicity (Cree vs. non-Natives) on infant macrosomia was determined after statistically controlling for differences between the two ethnic groups in age, parity, pregravid body weight or body mass index, height, gestational weight gain, GDM prevalence and smoking status.

These research questions are addressed in the form of three manuscripts (chapters 3, 4 and 5).

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CHAPTER 2
LITERATURE REVIEW

This literature review covers three major topics: gestational diabetes mellitus (GDM), infant macrosomia, and the epidemiology of GDM and macrosomia in North American Native populations. The chapter begins with an extensive review of GDM. Included in this review are the definition, pathophysiology, determinants and specific controversies related to the screening, diagnosis and treatment of GDM. This is followed by a critical review of the literature on risk factors of infant macrosomia. The chapter ends with a comprehensive review of the literature on the prevalence and predictors of GDM and infant macrosomia among Native peoples in North America. For this review, pertinent original publications and review articles published in English since 1966 were identified through an extensive literature search on MEDLINE. In addition, MEDLINE articles were carefully perused to identify other relevant publications in journals not listed in MEDLINE. In this review, preference was given to studies that were well-designed and recent (over the past 10 y).

2.1 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" (National Diabetes Data Group, NDDG 1979). The definition allows for the possibility of including undiagnosed Type 1 or Type 2 diabetes prior to pregnancy, and is irrespective of insulin treatment or persistence of diabetes after pregnancy (American Diabetes Association 1996). The prevalence of GDM in the general North American obstetric population is estimated to be between 3-5% (Magee et al 1993, Sermer et al 1995).

2.1.1 Pathophysiology of GDM

Normal pregnancy has characteristics of a "diabetogenic state", given the increased insulin resistance commonly seen in the late second and third trimesters (Kuhl 1991). The first half of pregnancy is characterized by increased insulin sensitivity, which facilitates maternal storage of fat and glycogen (Freinkel 1985). These serve as fuel reserves for the

fetus during the latter part of pregnancy. The second half of pregnancy is marked by increased insulin resistance due to increased placental secretion of anti-insulin hormones such as estrogen, progesterone, cortisol and human placental lactogen (Hollingsworth 1983). This results in an elevated level of circulating maternal substrates to meet the needs of the rapidly growing fetus. In a normal pregnancy, the net result of this metabolic shift is increased maternal secretion of insulin to maintain normal glycemic levels. GDM typically develops in the second half of pregnancy among women who are unable to adapt successfully to these changes. Lack of successful adaptation may be due to genetic predisposition to diabetes, which becomes manifest with the metabolic stress of pregnancy (Lucarini et al 1994), decreased insulin secretion, increased insulin resistance (Kautzky-Willer et al 1997, Persson et al 1997), or decreased insulin binding to receptors or a post-receptor defect (Kuhl et al 1985).

2.1.2 Predictors of GDM

Epidemiological evidence for predictors or risk factors for GDM is limited. Potential risk factors for GDM include advanced maternal age, pregravid obesity, body fat patterning, excessive gestational weight gain, ethnic origin, adverse obstetric history, family history of diabetes, dietary factors and a sedentary lifestyle. However, which of these pose independent risks for the development of GDM has not been adequately studied.

a) Age

Blood glucose values have been observed to rise with age independently of weight (Harris et al 1988). Therefore, the likelihood of having glucose intolerance during pregnancy also increases with age. Age was more strongly correlated with blood glucose levels than advancing gestation (weeks) in one study (Wilkerson and Sullivan 1963); in another study (Macafee and Beischer 1974), age ≥30 y was observed to be the strongest predictor of GDM. Marquette et al (1985) found that of the 12 women with GDM in their study, 10 were ≥25 y. McFarland et al (1985) reported that GDM prevalence increased with advancing age; the incidence of GDM was 8% among those <20 y (n=26), 20% for 20-24 y (n=60), 32% for 25-34 y (n=46) and 69% for 35-39 y (n=13). In a large population-based study, the incidence

of GDM was 0.7% among women <20 y vs. 3.8% among those >30 y (Coustan et al 1989), while another study reported an incidence of 1.18% among predominantly Black women <20 y (Lemen et al 1998). However, none of these studies accounted for the confounding effect of other risk factors for GDM such as body weight, parity or ethnicity.

Well-controlled studies report a significant independent effect of age on GDM. Dornhorst et al (1992) reported a relative risk for GDM of 2.9 (95% CI: 1.7-5.1) and 5.2 (95% CI: 2.8-9.5) among women of 25-34 y and ≥35 y compared with women <25 y, after adjusting for body mass index (BMI), ethnicity and parity. Berkowitz et al (1992) found that a 5 y increase in age increased the risk for GDM by 1.6 (95% CI: 1.5-1.8) after controlling for the effects of ethnicity, prepregnancy weight, prenatal care, history of infertility and family history of diabetes. In a large cohort of nurses (n=14,613) from 14 states in the United States (Solomon et al 1997), the independent effect of age (25-29 y, 30-34 y, 35-39 y and ≥40 y) on GDM was determined in multivariate analyses adjusting for the effects of family history of diabetes, ethnicity, pregravid physical activity, pregravid BMI and early adulthood weight gain. The risk for GDM was statistically significant only among women ≥40 y compared with women between 25-29 y (RR: 2.2, 95% CI: 1.3-4.0). The mechanism by which age raises glycemic levels independent of other factors remains to be elucidated.

b) Ethnicity

The incidence of GDM has been observed to be higher among some ethnic groups than others. In a study among 11,205 women in a multi-ethnic clinic in London, women from the Indian subcontinent had the highest relative risk for GDM (RR: 11.3, 95% CI: 6.8-18.8), followed by women from Southeast Asia (RR: 7.6, 95% CI: 4.1-14.1), the Middle East (RR: 5.9, 95% CI: 3.5-9.9) and Africa (RR: 3.1, 95% CI: 1.8-5.5) compared with local White women after adjustment for age, parity and obesity (Dornhorst et al 1992). In an ethnically heterogeneous sample of 10,187 women in the United States, the following ethnic groups had a significantly higher risk for GDM compared with Whites, after controlling for maternal age, prepregnancy weight, history of infertility, prenatal care and family history of diabetes: Orientals (RR: 2.6, 95% CI: 1.6-4.2), first generation Hispanics (RR: 1.6, 95% CI: 1.2-2.2), and Indian and Middle Eastern women (RR: 3.7, 95% CI: 1.9-7.4) (Berkowitz et al 1992).

Green et al (1990) observed a significantly higher incidence of GDM among Chinese (7.3%) and Hispanic women (4.2%) compared to Black (1.7%) and non-Hispanic White women (1.6%), after accounting for age and BMI. Similarly, in a multi-ethnic clinic in Chicago, the relative risk for GDM was 1.8 (95% CI: 1.1-2.9) among Black women and 2.5 (95% CI: 1.5-4.0) among Hispanic women compared with White women, after adjusting for age and percent ideal body weight (Dooley et al 1991). High rates of GDM have also been reported among some Aboriginal groups in Canada (Harris et al 1997) and the United States (Murphy et al 1993, Benjamin et al 1993, Rith-Najarian et al 1996) compared with the general North American population. Ethnic differences in GDM risk may reflect differences in genetic predisposition to diabetes (Neel 1962), ethnic differences in gastro-intestinal handling of glucose (Phillipou 1993, Schaefer et al 1972) or may be due to residual confounding by non-genetic factors which may be either overlooked, inadequately measured or controlled (Kaufman 1997).

c) Pregravid obesity

Obese pregnant women have higher fasting and post-prandial blood glucose and insulin levels compared with lean pregnant women (Roberts et al 1988, Borberg et al 1980, Hollingsworth and Ney 1992). High pregravid weight increases the risk for GDM, independently of age, parity and ethnicity (Berkowitz et al 1992, Dooley et al 1991, Dornhorst et al 1992). Berkowitz et al (1992) reported a relative risk of 1.1 (95% CI: 1.07-1.14) for every 10 lb increase in pregravid weight in a multi-ethnic sample, after controlling for the influence of age, race, prenatal care and medical history. In another study (Dornhorst et al 1992), the relative risks for GDM for women with a BMI (at booking) between 27-34 kg/m^2 or ≥ 35 kg/m^2 were 4.0 (95% CI: 2.9-5.6) and 8.9 (95% CI: 5.3-14.8), respectively, compared with those with BMI <27 kg/m^2, after adjusting for the effects of age, parity and ethnicity. In the Nurses' Health Study (Solomon et al 1997), the relative risk for GDM among US nurses was significantly increased among those with a pregravid BMI between 25-29 kg/m^2 (RR: 2.13, 95% CI: 1.65-2.74) or ≥ 30 kg/m^2 (RR: 2.9, 95% CI: 2.2-3.9) compared with nurses with a BMI <20 kg/m^2, after adjusting for age, weight gain in early adulthood, ethnicity, smoking status and family history of diabetes. The relative risks

obtained in this study might be overestimated, owing to comparison with an underweight (BMI <20 kg/m^2) rather than a normal-weight referent group (BMI between 20-25 kg/m^2).

Central obesity may impart a greater risk for GDM than overall obesity (Zhang et al 1995). Both pregravid and gravid central fat patterning have been linked with an increased risk for GDM. In a study of 720 singleton pregnancies (Zhang et al 1995), the risk for GDM was much higher among women with a high pre-pregnancy waist-hip (WHR) ratio than those with a high BMI, after adjusting for age, ethnicity (black/white), family history of diabetes and parity. Women in the highest tertile of WHR (tertile range: 0.74-1.02) had a relative risk of 4.0 (95% CI: 1.5-10.8) compared with women in the lowest WHR tertile (tertile range: 0.63-0.71), whereas women in the highest tertile of BMI (tertile range: 24.1-53.5 kg/m^2) had a relative risk of 1.9 (95% CI: 0.8-4.5) compared with those in the lowest BMI tertile (tertile range: 14.9-22.1 kg/m^2). In another study (Branchtein et al 1997), waist-to-hip ratio and waist circumference measured between 21-28 weeks gestation predicted an increased risk for GDM that was independent of the effects of age, height, skinfold thickness, ambient temperature, family history of diabetes, uterine height, skin color, obstetric history and prenatal care. A unit increase in waist-to-hip ratio or waist circumference (cm) increased mean 2-h plasma glucose levels on a 75 g glucose load by 1.85 mmol/L and 0.016 mmol/L respectively ($p<0.02$).

d) Pregnancy weight gain

Excessive weight gain during pregnancy may increase the risk for GDM. Indirect evidence for this comes from one study (Borberg et al 1980) which showed a smaller increase in fasting and meal stimulated plasma insulin concentration from 16 to 36 weeks gestation among obese non-diabetic women on an energy- and carbohydrate-restricted diet (n=8) compared with obese women on an unrestricted diet (n=10). The lower increase in insulin levels in the diet-restricted group paralleled their smaller weight gain over this period compared with the unrestricted group (5.1 ± 1.7 kg vs. 11.0 ± 3.6 kg). To our knowledge, no studies in the literature have evaluated the impact of gestational weight gain on risk for GDM. Total gestational weight gain cannot be evaluated as a predictor of GDM because treatment for GDM typically includes dietary modification and restriction of energy intake

and weight gain, especially for obese women with GDM. Rate of weight gain before GDM diagnosis should therefore be used in such analyses. The impact of prediagnostic rate of gestational weight gain on GDM risk remains to be investigated in population studies.

e) Stature

The effect of stature on GDM has been evaluated in few studies. Final adult stature is influenced by an individual's intra-uterine environment, post-natal environment and genetics (Davies 1981), and therefore an association of stature with GDM may be a reflection of the effect of any of these factors. An inverse association between stature and GDM has been described in some studies. Phillipou (1991), reported that short stature was a significant predictor of a positive GDM screen, in addition to Asian race, prepregnancy weight and maternal age. Jang et al (1998) reported a two-fold higher risk for GDM among short women ($\leq$157 cm) compared with tall women ($\geq$163 cm) (Odds ratio: 2.0, 95% CI: 1.4-3.0), after adjusting for age and BMI in a large cohort of Korean women (n=9005). In another study among 2772 Greek women (Anastasiou et al 1998), women with GDM were significantly shorter than normoglycemic women by 2.5 cm ($p<0.001$). The significant inverse association of height with GDM persisted after adjusting for the effects of age and BMI.

f) Family history of diabetes

Women with a family history of diabetes may be at a 2- to 3-fold higher risk for GDM compared with women without any such history (Mestman 1980). Martin et al (1985) reported that 44% of women with GDM had a parental history of diabetes compared to only 13% of normoglycemic women. As maternal diabetes was more common than paternal diabetes among GDM women than among women with pregestational diabetes or nondiabetic controls, the authors suggested that exposure to a diabetic intra-uterine environment, rather than genetic endowment, may increase susceptibility to GDM. Whether mothers of these GDM women had diabetes during pregnancy could not be determined, as neither the type of diabetes nor the age of onset could be ascertained with accuracy. However, findings of a study on Pima Indian women seem to support this speculation. Offspring of women who had diabetes during pregnancy had a higher prevalence of diabetes

compared with offspring of women who were nondiabetic during pregnancy but became diabetic after pregnancy (Odds ratio: 9.2, 95% CI: 1.1-77.0), after controlling for the effects of age, paternal diabetes and age of maternal onset of diabetes (Pettitt et al 1993).

g) Obstetric history

An adverse obstetric history is associated with an increased risk for GDM. In a study among 10,187 multi-ethnic women (Berkowitz et al 1992), the prevalence of GDM increased with a history of infertility, previous premature birth and stillbirth. However, of these only a history of infertility remained significant in multivariate analyses controlling for the effects of maternal age, race, prepregnancy weight and a family history of diabetes (RR: 1.8, 95% CI: 1.1-2.8). McGuire et al (1996) studied risk factors for GDM in 1375 women with GDM and 6380 women without diabetes. After adjustment for maternal age, women who had a macrosomic infant (>4000 g) in their previous pregnancy but no history of GDM were almost twice as likely to have GDM in the subsequent pregnancy as nondiabetic women who delivered normal- or low-birth-weight babies in their previous pregnancy (Odds ratio: 1.8, 95% CI: 18.9-36.9). Women who had GDM in their previous pregnancy and delivered a normal weight infant were 26 times more likely to have GDM in the current pregnancy (Odds ratio: 26.4, 95% CI: 18.9-36.9). The risk was also significantly elevated for women who had both GDM and macrosomic babies in their previous pregnancy (Odds ratio: 23.3, 95% CI: 11.9-45.5). Other studies evaluating the risk for GDM in a subsequent pregnancy among women with GDM in the index pregnancy report that the risk for GDM recurrence increased among women who delivered macrosomic babies (Philipson and Super 1989, Gaudier et al 1992), had a high prepregnancy BMI, or required insulin therapy (Gaudier et al 1992).

h) Diet

Various studies have attempted to identify an etiologic link between various dietary components and the development of Type 2 diabetes. In a large cohort of men (Salmeron et al 1994), the risk for Type 2 diabetes was increased with increased consumption of carbohydrates having a high glycemic index and decreased with high intake of magnesium

and cereal fibre. The inverse association between cereal fibre intake and risk for Type 2 diabetes was confirmed in a similar study among female nurses in the US (Salmeron et al 1997), after accounting for the effects of BMI, age, smoking, physical activity, alcohol, and total energy intake. An earlier study among the same cohort of women reported an inverse relationship between vegetable fat, potassium, calcium and magnesium intakes and the risk of occurrence of Type 2 diabetes (Colditz et al 1992). Increased total energy and starch intake was associated with high diabetes rates in a study on Pima Indian women (Bennett et al 1984). In contrast, another study among a Native group in Canada found no significant association of energy intake, dietary starch, fat or simple sugars with Type 2 diabetes. However, in multivariate analyses adjusting for the effects of age, BMI and gender, the latter study found that high protein intakes increased the risk for Type 2 diabetes whereas increased fibre intake had a protective effect (Wolever et al 1997). It appears from these studies that dietary fibre may have a protective effect on diabetes, but the effects of other dietary components on diabetes risk remain to be ascertained.

No studies have attempted to investigate the relationship between diet and GDM from a causal perspective. Existing studies have mainly evaluated the effectiveness of varying levels of energy intake, macronutrient or micronutrient intakes in GDM treatment (Hollingsworth and Ney 1992, Jovanovic-Peterson et al 1990, Algert et al 1985, Jovanovic-Peterson and Peterson 1996). The role of dietary components in risk for GDM remains to be determined.

i) Physical activity

Cardiovascular exercise is known to increase glucose disposal by increasing insulin sensitivity and binding to receptors (Schneider et al 1984, Wake et al 1991). Several well-controlled studies have demonstrated the protective effect of increased physical activity on Type 2 diabetes (Manson et al 1991, Helmrich et al 1991). Although two randomized trials among women with GDM clearly showed the benefits of exercise in maintaining euglycemia (Jovanovic-Peterson et al 1989, Rosas and Constantino 1992), the effect of physical activity during pregnancy on GDM risk has not been adequately investigated at the population level. An accurate description of this relationship may be hampered by potential changes in

physical activity patterns of women during pregnancy, which may not reflect their usual physical activity patterns, or by the use of imprecise measures to estimate physical activity in large population studies. The existing evidence for the role of physical activity in GDM is inconclusive. In a cohort of 14,613 nurses in the United States (Solomon et al 1997), pregravid physical activity was determined from a questionnaire which enquired about the frequency, duration and intensity of different activities. After adjusting for the effects of age, pregravid BMI, family history of diabetes, smoking and weight gain during early adulthood, the inverse association between pregravid physical activity and GDM was no longer statistically significant. In another retrospective study of 12,799 women (Dye et al 1997), the risk for GDM was lower only among extremely obese women (BMI >33 kg/m^2) who exercised at least once per week for 30 minutes or more during pregnancy compared with their obese counterparts who did not exercise (Odds ratio: 1.9, 95% CI: 1.2-3.1). This effect was not evident among women with BMI ≤ 33 kg/m^2. Exercise patterns of women in this study were obtained from a questionnaire which elicited information on frequency of participation in exercise per week for at least 30 minutes. Inconsistent results between the two studies may be due to differences in the population characteristics, methods of assessment of physical activity or determination of physical activity in the pregnant vs. non-pregnant state.

In conclusion, ample evidence exists for the risk posed by advanced maternal age and an adverse family history of diabetes for the development of GDM. However, these factors are not modifiable. In order to help prevent the onset of GDM, greater emphasis needs to be placed on understanding the contribution of modifiable risk factors such as pregravid weight, pregnancy weight gain, dietary intake and physical activity patterns to the disease.

2.1.3 GDM Screening, Diagnosis and Treatment: Controversies

Screening and treatment for GDM is a widely disputed issue, and several reviews have been published on this subject (Coustan 1994, Thompson 1996, Okun et al 1997a). Specific areas of controversy include whom to screen, what screening and diagnostic criteria should be used, what treatment strategy should be used and the effectiveness of screening and treatment in alleviating any adverse maternal or perinatal outcomes. These issues are

discussed in the following sections:

a) Whom to screen?

Debate regarding the population to be screened for GDM is compounded by uncertainty regarding the clinical significance of the disorder and benefits of screening. The lack of consensus is reflected in the different screening strategies proposed by different authoritative groups in North America in the past. Traditionally, identification of women at risk for GDM was based on the presence of one or more of historical or clinical risk factors such as previous still birth, miscarriage, macrosomia, or GDM, family history of diabetes, advanced age, or obesity. Selective screening for GDM based on the presence of one or more of these risk factors was recommended by the American College of Obstetricians and Gynecologists (ACOG) (1994a) and the Canadian Task Force on the Periodic Health Examination (1992). However, such a screening strategy could miss anywhere between one-third to one-half of women with GDM (Coustan et al 1989, Massion et al 1987, Lavin 1985). Therefore, the American Diabetes Association (ADA) (1986) and the Society of Obstetricians and Gynecologists of Canada (SOGC) (1992) recommended universal screening. More recently, an international expert committee appointed by the ADA (1997) reviewed the scientific evidence for and against universal screening and concluded that universal screening was not cost-effective. The committee recommended selective screening of women based on the presence of one or more of the following risk factors for GDM: a) age >25 y; b) obesity; c) non-White ethnicity d) family history of diabetes. These guidelines have been endorsed by the ADA, ACOG (ADA 1997) and the Canadian Diabetes Association (CDA) (1998a).

b) Screening and diagnostic criteria

There is no international consensus regarding criteria for screening or diagnosis of GDM. In North America, the most widely used screening and diagnostic criteria are those recommended by the National Diabetes Data Group (NDDG 1979) or the World Health Organization (WHO 1985). The ACOG and the ADA currently recommend screening and diagnosis of high-risk women for GDM by the two-step procedure of the NDDG (NDDG

1979). Specifically, high risk women are screened with a 1-h 50 g oral glucose challenge test (OGCT) regardless of time of day. A positive screen (1-h plasma glucose ≥7.8 mmol/L) is followed by a 3-h 100 g oral glucose tolerance test (OGTT) in the fasting state. GDM is diagnosed if any two of the four threshold values on the OGTT are met or exceeded: fasting, 5.8; 1-h, 10.6; 2-h, 9.2; and 3-h, 8.1; mmol/L. The CDA (1998a) recommends the use of either the NDDG criteria or the 75 g 2-h OGTT recommended by the WHO but with the following modifications: GDM is diagnosed if 2 of the following 3 thresholds on the 2-h 75 g OGTT are met or exceeded: fasting, 5.3; 1-h, 10.6; 2-h, 8.9; mmol/L. If only one value is met or exceeded the diagnosis is impaired glucose tolerance (IGT).

The NDDG criteria for GDM screening and diagnosis are modifications of diagnostic criteria for GDM originally established by O'Sullivan and Mahan (1964). In their original work, a large cohort of 752 pregnant women underwent a 1-h 50 g OGCT followed by a 3-h 100 g OGTT. The best threshold value was identified as the mean + 2 SD at each stage of the OGTT, and a positive diagnosis was based on two abnormal OGTT values (O'Sullivan and Mahan 1964). Validation of these criteria was based on the ability to predict subsequent diabetes in a second cohort of women (n=1013) who underwent the OGTT during pregnancy and were tested annually for non-pregnant diabetes for up to 8 years. The positive predictive value of the diagnostic criteria for subsequent diabetes was determined to be 36.1% (O'Sullivan and Mahan 1964). The sensitivity and specificity of the 1-h 50 g screen using a cut-off of 7.2 mmol/L for glucose levels in whole blood were 79% and 87%, respectively (O'Sullivan et al 1973a). In a subsequent study (O'Sullivan et al 1973b), these investigators evaluated perinatal outcomes among women with GDM diagnosed by these criteria and observed increased perinatal mortality rates among older (≥25 y) and heavier (≥120 % ideal body weight) women with GDM (10.1%) compared with normoglycemic controls (2.9%) ($p<0.05$). However, these studies had several drawbacks including selection bias and failure to determine the effect of GDM on infant mortality independent of age and body weight.

Based on this original work, the NDDG modified the diagnostic criteria to reflect plasma glucose rather than whole blood glucose thresholds and rounded these to the nearest 0.28 mmol/L. The NDDG criteria have been criticized because they were derived from a study with questionable validity. Other criticisms include poor reproducibility of the

diagnostic test (Naylor 1989), the need for 4 blood drawings, a high glucose load which may cause nausea in pregnant women and lack of comparability with the post-partum 2-h 75 g glucose tolerance test for diabetes (Pettitt et al 1994).

The other test widely used to diagnose GDM internationally is the 75 g 2-h OGTT recommended by the WHO (WHO 1985). GDM is diagnosed if either the fasting or the 2-h value exceeds 7.8 mmol/L or 11.1 mmol/L. IGT is diagnosed if the fasting value is <7.8 mmol/L and the 2-h value is between 7.8 and 11.1 mmol/L. The advantage of the WHO test is that it requires only 2 blood drawings, involves a smaller glucose load (75 g) and is comparable to the post-partum test for Type 2 diabetes.

Few studies have determined the comparability of the WHO vs. the NDDG criteria in predicting adverse materno-fetal outcomes. The comparability of these criteria in predicting infant macrosomia and cesarean section rates was assessed in a study among the Pima Indians of Arizona (Pettitt et al 1994). Of 127 pregnant non-diabetic Pima women who underwent a 75 g 2–h OGTT, those with an elevated 1-h value (≥7.8 mmol/L, n=42) were asked to undergo a 3-h 100 g OGTT. The WHO criteria correctly identified as abnormal 38% of the women who delivered macrosomic infants and 57% of cesarean sections compared with 6.3% and 0% respectively by the NDDG criteria. Owing to the small sample size, no firm conclusions can be drawn from this study. In another study (Weiss et al 1998), the comparability of glycemic levels on a 2-h 75 g OGTT or a 2-h 100 g OGTT was compared among women with GDM (n=30) and those with normoglycemic status (n=30); women in each group were randomly assigned to one of the tests. The results indicated that women with GDM had similar fasting and 1-h plasma glucose levels on the 75 g or 100 g glucose load, but the 2-h value was 0.89 mmol/L higher for the 100 g load. Among control women, plasma glucose levels were different at 1 and 2 h between glucose loads. A major limitation of this study is that GDM diagnosis was based on a single capillary value (≥8.9 mmol/L), which can result in significant misclassification.

Several studies have attempted to identify screening tests with better sensitivity and specificity than the currently recommended 1-h 50 g OGCT. The 50 g OGCT does not require fasting, is inexpensive, moderately sensitive and reproducible. However, some recent studies indicate that the time elapsed since the last meal may affect the sensitivity of the test

(Sermer et al 1994, Coustan et al 1986). Other screening tests which have been evaluated for their usefulness are glucosuria, glycosylated hemoglobin and glycosylated plasma proteins (fructosamine). Owing to the lower renal threshold for glucose during pregnancy and wide intra- and inter-individual variation, glucosuria has been acknowledged to have poor sensitivity as a screening tool for GDM (Garner 1995). Urinary glucose measurement was reported to have a sensitivity of less than 30% in one study (Lind and Anderson 1984). Glycosylated hemoglobin (GHb) has been found to be a useful tool for monitoring glycemic control in diabetes (Bunn 1981, O'Shaughnessy 1981). Although the ease of testing makes it a potentially useful measure for GDM screening, the lack of sensitivity to relatively short-term glycemic excursions in GDM compared to non-pregnant diabetes (Cousins et al 1984) and the significant overlap of GHb values between women with and without GDM make it a less sensitive test compared with the standardized OGCT (Loke et al 1994, O'Shaughnessy et al 1979, Cousins et al 1984). Of the various glycosylated plasma or serum proteins, fructosamine has been extensively evaluated as a screening tool for GDM. In a study of 682 multiethnic subjects in the Middle East (Hughes et al 1995), serum fructosamine levels measured at 26-32 weeks gestation had a sensitivity of 79.4% and a specificity of 77.3% in detecting GDM diagnosed using modified NDDG criteria. In contrast, other studies report poor sensitivity of fructosamine as a screening test for GDM compared with the 50 g OGCT (Roberts et al 1990, Menon et al 1991).

Other investigators have used modified versions of the NDDG or WHO criteria in assessing materno-fetal outcomes. Carpenter and Coustan (1982) have suggested lowering the NDDG thresholds by 0.56 mmol/L for fasting, 1-h and 2-h plasma glucose values and by 0.28 mmol/L for the 3-h plasma glucose value, which are more accurate conversions of threshold glucose values from whole blood to plasma. Although an additional 50% of cases were identified by the modified criteria, the frequency of perinatal morbidity was similar to cases diagnosed by the NDDG criteria (Magee et al 1993). Berkus et al (1995) evaluated the incidence of large-for-gestational age (LGA) infants among 708 women (>30 y) who screened normal for GDM by the NDDG criteria. Three criteria for GDM were then used to reclassify these women: a) Coustan criteria: fasting value ≥5.3, 1-h ≥10.0, 2-h ≥8.6 and 3-h ≥7.8 mmol/L (any 2 abnormal values); b) Langer criteria: any one abnormal value by the

NDDG thresholds; and c) Sacks criteria: ≥5.3, ≥ 9.5, ≥ 8.4 and ≥ 7.3 mmol/L at each of the OGTT time points respectively (any 2 abnormal values). GDM women by the Coustan and Langer criteria had a higher proportion of LGA infants compared with control women, whereas the difference was not significant by the Sacks criteria. The authors conclude that the Coustan and Langer criteria were as efficient as the NDDG criteria in identifying LGA infants, whereas the Sacks criteria were less satisfactory. A GDM group diagnosed by the NDDG criteria was not included to support this. Further, although women with GDM by each of these criteria were significantly older than the controls, this was not controlled in the analyses.

Sacks et al (1995) advocate the use of 75 g OGTT with blood sampling at fasting, 1 and 2 hours post-challenge. They recommend cut-offs of 5.6 mmol/L, 10.8 mmol/L and 8.9 mmol/L at the 3 time points, requiring at least two of the three values to be exceeded for a positive diagnosis. The use of these criteria resulted in a GDM incidence of 3.2% in their study sample compared to 3.4% by the NDDG criteria in another sample studied at the same institution. Women who exceeded these criteria had more macrosomic infants than those who did not. However, the authors acknowledge that other combinations of threshold values yielded similar results indicating the lack of a clear demarcation of maternal glucose levels above which the risk for pathological outcomes increases.

In summary, the current gold standards for the screening and diagnosis of GDM are the ones recommended by the NDDG or the WHO. The benefits of using other screening or diagnostic tests as yet remain unproven. The comparability of the NDDG and the WHO tests in predicting adverse materno-fetal outcomes warrants further investigation.

c) Treatment strategies

The goal of treatment in GDM is to normalize blood glucose levels and decrease adverse maternal and fetal outcomes associated with hyperglycemia. Dietary intervention is the first line of treatment for GDM. Other treatment strategies, which may be used in combination, include insulin therapy, exercise and blood glucose monitoring.

i. Energy restriction

There is very limited information available on the effects of energy restriction on pregnancy outcomes. Energy restriction has been recommended for obese women with GDM; the aim is to optimize blood glucose levels through restriction of gestational weight gain. Weight gain restriction in obese pregnant women with GDM is also advantageous in minimizing post-partum weight retention and risk for subsequent diabetes (Dornhorst et al 1990).

Most clinicians recommend the use of moderate energy restriction (100 kJ/kg ideal body weight, 6276-7531 kJ/day) in treating obese women with GDM (Gunderson 1997). Moderate energy restriction clearly helps minimize gestational weight gain and maintain euglycemia but the effect on infant birth weight is equivocal. Algert et al (1985) compared infant birth weight between obese GDM women (BMI $\geq$27 kg/m^2) (n=22) on an energy restricted diet (7113-7531 kJ/day), lean GDM women (n=31) who were instructed to consume 8368-12,552 kJ/day and normoglycemic controls (n=10) on an unrestricted diet. Despite good glycemic control, lower reported energy intake and lower weight gain, obese women with GDM had bigger babies compared with lean women with GDM and normoglycemic women (3922 $\pm$ 662 g vs. 3544 $\pm$ 588 g and 3448 $\pm$ 303 g respectively, $p<0.03$).

In another study (Dornhorst et al 1991), infant birth weight was compared between 35 women with GDM treated with a 5021-7531 kJ diet (84-126 kJ/kg ideal body weight), 35 women with a negative glucose screen and 35 women with a positive glucose screen but normal diagnostic test who did not receive any dietary advice. The latter groups were matched with GDM women for age, parity, BMI and ethnicity. Further, 2337 consecutive deliveries from the general obstetric population (non-diabetic) were also used as an external control. Weight gain after 28 weeks gestation was discouraged among women with GDM. Twenty four of the 35 women with GDM were obese (BMI $\geq$27 kg/m^2). Average birth weight and incidence of macrosomia ($\geq$4000 g) was similar between the treated GDM group, the general obstetric controls and the screen-negative controls but was significantly higher among the screen-positive controls. Infant birth weight was not compared between obese and non-obese women with GDM in this study. No firm conclusions can be drawn from these

two studies owing to the small sample sizes. Also, the generalizability of these findings is limited to women with lesser degrees of glucose intolerance, as women who required insulin treatment for glycemic control (n=8) were excluded from the study by Dornhorst et al (1991), and only 2 obese GDM women in the study by Algert et al (1985) were treated with insulin.

Severe energy restriction ($\leq$5021 kJ/day) is not recommended for pregnant women because it can retard fetal growth (Gunderson 1997) and cause ketosis, which has been implicated in subsequent impairment of cognitive functioning (Rizzo et al 1991). In a randomized trial (Magee 1990), obese GDM women were randomly assigned to a diet of 10,042 kJ/day (n=5) or 5021 kJ/day (n=7). Twenty-four hour mean glycemic levels were significantly lower in the energy restricted group compared to the control group ($p<0.01$), but the energy-restricted group had pronounced ketonuria and high levels of fasting plasma β-hydroxybutyrate. Limitations of this study include small sample size and no evaluation of pregnancy outcomes.

ii. Carbohydrate restriction

High post-prandial glucose levels have been shown to increase the risk for infant macrosomia (Jovanovic-Peterson et al 1991, Parfitt et al 1992). Some clinicians therefore recommend restriction of carbohydrate to reduce post-prandial glucose peaks but not so severe as to cause ketonemia, hypoglycemia or fetal growth retardation (Gunderson 1997). However, there is no consensus regarding the need or degree of carbohydrate restriction. While some recommend a macronutrient breakdown of total energy intake as 50-60% carbohydrate, 15-20% protein and 30% fat (Hollingsworth and Ney 1992), others recommend a diet more restricted in carbohydrate, comprising 40% carbohydrate, 40% fat and 20% protein (Jovanovic-Peterson 1990). The current recommendations by the ADA (1996) for pregnant diabetic women specify that energy intake from protein should constitute 10-20% of total energy intake but the remaining 80-90% of calories can be distributed over carbohydrate and fat, depending on individual needs. Because of diurnal variations in plasma cortisol and glucagon, morning hyperglycemia is frequently observed among women with GDM and therefore a breakfast restricted in carbohydrates is recommended (Hollingsworth 1983).

Two recent studies using women with GDM indicated the potential for normalizing birth weight by achieving good glycemic control through carbohydrate restriction. In one study (Major et al 1998), 42 women with GDM were non-randomly assigned either to a diet comprising <42% or 45-50% of total calories as carbohydrate. Group assignment was based on the day of clinic visit. Demographic and constitutional characteristics were similar between the two groups. Women in the <42% carbohydrate group had lower post-prandial glycemic levels after 6 weeks of treatment (6.1 ± 0.99 vs. 7.3 ± 1.0 mmol/L, $p<0.04$), lower mean infant birth weight (3694 ± 378 g vs. 3890 ± 455 g), lower risk for large-for-gestational age infants (9% vs. 42%, RR: 0.22, 95% CI: 0.05-0.91), fewer cesarean section deliveries for cephaopelvic disproportion and macrosomia (RR: 0.15, 95% CI: 0.04-0.94) and fewer women required insulin therapy (RR: 0.14, 95% CI: 0.02-1.00) compared with the less restricted group. It is unclear whether total energy intake was similar in the two groups.

In another study (Snyder et al 1994), 353 women with GDM were prescribed diets based on a total energy intake of 146 kJ/kg ideal body weight/day, with carbohydrate, fat and protein comprising 34%, 47% and 19% of total energy intake, respectively. Dietary treatment alone significantly decreased fasting plasma glucose levels (4.36 ± 0.52 mmol/L to 4.11 ± 0.44 mmol/L, $p<0.001$) and rate of weight gain (0.35 ± 0.18 kg/wk to 0.16 ± 0.35 kg/wk, $p<0.001$) but not post-prandial glucose levels (5.85 ± 1.29 mmol/L, $p=0.86$) from pre-treatment values. A decline in post-prandial glucose levels was seen only among those who were treated with insulin in addition (7.18 ± 1.77 mmol/L to 6.42 ± 0.98 mmol/L, $p<0.001$). The average birth weight was 3542 ± 481 g, and 13.8% of the infants were macrosomic (≥4000 g), which are similar to that seen in the general population. Both maternal fasting and post-prandial glucose levels were significantly and independently associated with infant birth weight after adjusting for the effects of maternal age, parity, gestational duration, BMI, rate of weight gain before and after GDM diagnosis, mode of treatment (diet or diet and insulin), and total energy intake.

Besides the total amount of carbohydrate, the source of carbohydrate may also be important. Complex carbohydrates produce smaller glycemic excursions and therefore should make up the bulk of the carbohydrate consumed (Jenkins et al 1984). The glycemic index of foods, the exchange system and carbohydrate counting are some of the dietary

strategies employed by dietitians/nutritionists in educating individuals with diabetes to make food choices based on the carbohydrate content and glycemic response to different foods (Kalergis et al 1998). The current guidelines by the ADA and CDA (ADA 1998, CDA 1998b) for individuals with Type 1 and 2 diabetes, permit substitution of sucrose for other carbohydrates, up to a maximum of 10% of total energy intake. No specific recommendations were made for women with GDM.

iii. Meal pattern

There is insufficient evidence to make any specific recommendations regarding meal patterns for GDM. Practices vary between clinicians, however, most recommend distribution of total energy and carbohydrates over three meals and three snacks (Fagen et al 1995, Kitzmiller 1993). The CDA recommends the use of snacks which provide "15% of total daily energy intake and contain at least 25 g complex carbohydrate combined with more slowly digestible protein and fat" and especially a bedtime snack to prevent nocturnal hypoglycemia (CDA 1991). The current ADA guidelines do not include specific recommendations for either nutrient composition or meal patterns for women with GDM; rather, individualized dietary modifications and meal plans are recommended (ADA 1998).

The rationale for including snacks is to spread the carbohydrate load throughout the day. In one study (Jenkins et al 1992), glycemic and insulin profiles improved with increased meal frequency among individuals with Type 2 diabetes. However, studies evaluating effects of meal frequency on metabolic profiles among women with GDM are lacking. Hollingsworth and Ney (1992) caution against the use of daytime snacks in obese women with GDM as they elicit a higher post-prandial glucose and insulin response.

iv. Insulin therapy

Insulin therapy is usually initiated if dietary treatment alone is not successful in maintaining pre-prandial and/or post-prandial euglycemia. Oral hypoglycemic agents are not recommended during pregnancy as they can have teratogenic effects on the fetus (Smithberg and Runner 1963). Glycemic thresholds for initiation of insulin therapy vary across studies. Target glycemic levels recommended by the CDA (1998a) to achieve optimal neonatal

outcome in GDM are fasting: <5.3 mmol/L, 1-h post-prandial: <7.8 mmol/L and 2-h post-prandial: <6.7 mmol/L. Insulin therapy is recommended if these target levels are not achievable on diet therapy alone. The ADA (1996) recommends initiation of insulin therapy if plasma fasting glucose exceeds 5.8 mmol/L or 2-h post-prandial value exceeds 6.7 mmol/L on two or more occasions over a 1-2 week period. The use of human rather than animal insulin is recommended in pregnancy, as it is causes less severe glycemic excursions (Jovanovic-Peterson et al 1992) and is less allergenic to the fetus (Reece et al 1995). The choice of insulin, frequency of administration and dosage varies according to individual needs in maintaining euglycemia. Studies evaluating the effectiveness of diet and insulin therapy vs. diet therapy alone are equivocal, with some reporting improved pregnancy outcomes with insulin treatment (Coustan and Imarah 1984, Thompson et al 1990) and others reporting no difference (Garner et al 1997, Li et al 1987).

v. Self-monitoring of blood glucose (SMBG)

SMBG is an important aspect of GDM management, especially for women on insulin therapy, as it provides immediate feedback regarding glycemic levels, aids fast recognition of hypo- or hyper-glycemia, helps in better control of blood sugar, and reinforces the relationship between portion sizes, food choices and glycemic levels (Fagen et al 1995). Reflectance meters are recommended rather than visual readings of blood glucose test strips, as they are more quantitative and accurate (Langer et al 1994). Drawbacks of SMBG include cost of the meters and strips, inaccurate readings owing to poor calibration or inadequate volume of blood sample and pain (CDA 1998c).

There is no standard regarding frequency or timing of SMBG. Intensive SMBG using visual strips or reflectance meters helps in the identification of more patients requiring insulin therapy, results in more stringent glycemic control and a decreased incidence of infant morbidity (Goldberg et al 1985, Langer et al 1994). Also, post-prandial rather than pre-prandial SMBG may improve pregnancy outcome in women with GDM. De Veciana et al (1995) randomly assigned 66 women with insulin-treated GDM to a regimen comprising either pre-prandial or post-prandial SMBG (before breakfast or 1-h after each meal). Women on the post-prandial regimen received significantly more insulin, had lower glycosylated

hemoglobin levels before delivery, lower infant mean birth weight, decreased incidence of large-for-gestational age infants, lower cesarean section rates for cephalo-pelvic disproportion and a lower frequency of neonatal hypoglycemia compared to women on the pre-prandial regimen. There were no small-for-gestational age (SGA) infants in the pre-prandial group and only 1 SGA infant in the post-prandial group. The authors suggest that post-prandial monitoring of blood glucose helps achieve tighter glycemic control in GDM. Generalizability of the study findings is limited because the study subjects were predominantly Hispanic and were all treated with insulin, indicating more severe glucose intolerance.

vi. Exercise

Increased physical activity may improve glycemic levels indirectly by impacting on energy metabolism and body weight or directly by enhancing insulin sensitivity and glucose uptake by peripheral tissues (Schulz and Weidensee 1993, Wake et al 1991). The latter effect is seen even after a single episode of exercise (Devlin et al 1987), indicating that improved glucose clearance may be due to the cumulative effects of individual exercise episodes rather than a training effect (Schneider et al 1984).

Uncertainty still prevails regarding safe and optimal levels of exercise among pregnant women. Current evidence indicates that moderate intensity exercise during pregnancy does not increase the risk for adverse outcomes for low risk women (ACOG 1994b). Exercises that do not cause uterine contractions, fetal bradycardia or maternal hypertension are regarded as safe during pregnancy. In one study (Durak et al 1990), fetal heart rate, maternal blood pressure and uterine activity were measured in healthy pregnant women during exercise using a bicycle, recumbent bicycle, rower, treadmill or arm-ergometer. Of the 5 types of equipment, the upper-arm ergometer was judged to be the safest.

Studies evaluating the safety and utility of exercise among women with GDM as a means of maintaining euglycemia are very limited. Rosas and Constantino (1992) randomly assigned 41 women with class A2 GDM (fasting plasma glucose between 5.8-7.1 mmol/L) to treatment involving dietary modification and a supervised exercise regimen or diet and insulin therapy. Women in the diet-exercise group performed supervised moderate intensity

exercise on a treadmill or bicycle ergometer 3 times/week, each session lasting 45 minutes. Pregnancy outcomes were similar between the two groups. The authors suggest that supervised exercise among women with GDM may be used as a safe alternative to insulin therapy. Jovanovic-Peterson et al (1989) randomized 20 women with GDM to a treatment of intensive diet therapy for 6 weeks or 6 weeks of diet therapy and supervised upper-body exercise using an arm-ergometer 3 times/week, each session lasting 20 minutes. At the end of the treatment period, women in the exercise group had significantly improved blood glucose profiles compared with those in the diet-only group ($p<0.001$). No pregnancy outcomes were evaluated in this study. In conclusion, moderate intensity exercise appears to be safe and beneficial for GDM women with different degrees of glucose intolerance. However, this finding needs to be confirmed in randomized clinical trials using larger numbers of women.

d) Is screening and treatment for GDM effective?

Despite widespread screening and treatment for GDM practiced by most health centers in North America, debate still rages over the benefits of screening and treatment of GDM for the woman or her infant. Purported benefits of screening and treatment for GDM include reduced perinatal mortality, morbidity and early identification and intervention for individuals at risk for Type 2 diabetes. However, the evidence for the effectiveness of GDM screening and treatment in improving immediate pregnancy outcomes is equivocal; results of existing studies are summarized in Table 1.

The use of perinatal mortality as an outcome measure is limited, given the recent decline in perinatal mortality rates in the general population (Persson et al 1985) and the very large sample size required to detect a meaningful change in perinatal mortality rates as a consequence of GDM screening or treatment. Studies which have evaluated the effect of GDM screening or treatment on perinatal mortality report that screening (Santini & Ales 1990) or treatment of GDM (O'Sullivan and Mahan 1966, Coustan and Imarah 1984) does not affect perinatal mortality.

Infant macrosomia is the most frequently used indicator of adverse perinatal outcome in maternal diabetes owing to its association with cesarean section, shoulder dystocia and

birth trauma (Stephenson 1993). A majority of studies testing the effect of any GDM treatment vs. no treatment consistently indicate that macrosomia rates are significantly lower among treated vs. untreated women (O'Sullivan and Mahan 1966, Naylor et al 1996, Rey et al 1996, Adams et al 1998, Coustan and Lewis 1978). In contrast, studies comparing different treatment strategies either report no difference in macrosomia rates between treated groups (Garner et al 1997, Persson et al 1985, Coustan and Lewis 1978) or less macrosomia in the diet and insulin treated vs. diet treated group (Coustan & Imarah 1984, Mello et al 1997) or intensively treated vs. conventionally treated group (Langer et al 1994). Part of the reason for these inconsistencies may be due to methodological flaws. The observational design of most studies with non-random treatment assignment could potentially lead to confounding with more motivated women opting for more stringent treatment (Coustan and Imarah 1984, Langer et al 1994). The randomized trials were also prone to such problems as potential for confounding due to incomplete randomization (Persson et al 1985, Garner et al 1997), or use of uncommon diagnostic criteria (Coustan and Lewis 1978, Persson et al 1985, Garner et al 1997).

The effects of GDM treatment on infant metabolic complications such as hypoglycemia, polycythemia, hyperbilirubinemia and respiratory distress have not been investigated to the same extent as macrosomia. Nevertheless, as with macrosomia, untreated GDM appears to carry an increased risk for infant metabolic problems compared with treated GDM or normoglycemic controls (Rey et al 1996, Adams et al 1998), whereas treatment with diet alone vs. diet and insulin appears to make little or no difference (Coustan and Imarah 1984, Persson et al 1985, Garner et al 1997). However, one study (Langer et al 1994) using a more intensive treatment strategy including frequent insulin therapy demonstrated lower rates of metabolic complications compared to conventional treatment with less frequent insulin use. The results of these studies need to be interpreted with caution given the potential for bias if only symptomatic infants are tested (Stephenson 1993).

The effectiveness of GDM treatment in preventing long-term adverse outcomes is not known. Approximately 20 to 80% of women with GDM, may develop Type 2 diabetes eventually (Damm et al 1992, Kjos et al 1995, Kaufmann et al 1995, Peters et al 1996) and the infants of these women are also at increased risk for subsequent obesity and diabetes

(Siverman et al 1991, Pettitt et al 1993), but there is no evidence that treatment of GDM helps reduce this risk. However, screening for GDM may aid in the early identification of individuals at risk for Type 2 diabetes, permitting timely intervention to prevent or delay the onset of this disease (Bennett and Knowler 1984, Pan et al 1997, Simmons 1996). Indirect evidence for this comes from a randomized trial in China (Pan et al 1997), in which men and women with impaired glucose tolerance (n=577) were randomly assigned to a no-intervention group (control) or one of 3 intervention groups: diet only, exercise only, or diet and exercise. A bi-yearly follow-up over a 6 y period revealed that the cumulative incidence of Type 2 diabetes was significantly lower among each of the three intervention groups compared with the control group (43.8%, 41.1% and 46.0%, respectively, vs. 67.7%, $p<0.05$). The rate of progression to Type 2 diabetes was significantly lower among the intervention groups even after adjusting for differences in baseline BMI and fasting glucose.

Diagnosis and treatment for GDM also has potential for negative effects which need to be carefully investigated. Adverse effects associated with a 'diagnostic label' include poor health perception among women with a false positive test for GDM (Kerbel et al 1997), and among those diagnosed with GDM; increased anxiety regarding fetal health (Laplante 1992), and high primary cesarean section rates (Naylor et al 1996). Very stringent treatment for GDM can also increase the risk for intra-uterine growth retardation (Langer et al 1989).

In conclusion, the evidence for effectiveness of GDM treatment in improving pregnancy outcomes is equivocal. Given that intervention for GDM includes methods to control glycemic levels as well as more intensive prenatal monitoring, it is unclear which intervention is truly beneficial in improving perinatal outcome (Okun et al 1997a). The observational design of most studies and lack of true randomization makes it difficult to evaluate the efficacy of one treatment over another or even over no treatment. The ideal study would be to randomly assign a group of GDM women to treatment or no treatment and evaluate short-term and long-term maternal and infant morbidity. However, owing to the established practice of treating all women identified with GDM, such studies may not be ethically feasible. The usefulness of GDM diagnosis or treatment in alleviating either short-term or long-term maternal and infant complications remains to be demonstrated in future well-controlled studies.

Table 1. Effects of GDM Treatment on Immediate Outcomes of Pregnancy

Study	Design & Intervention	Diagnostic Criteria	Sample Size	Results	Comments
O'Sullivan et al (1965)	-Randomized trial -treatment vs. no treatment vs. nondiabetic controls	O'Sullivan & Mahan criteria	N=307 (treated GDM) N=308 (untreated GDM) N=328 (nondiabetic controls)	-Fetal and neonatal death rates were not different between treated and untreated GDM cases but were significantly higher among both groups combined vs. controls -Infant macrosomia was three times higher among untreated GDM vs. treated GDM or controls	-Screen status of controls unclear -No control for confounding while comparing treated or untreated cases to controls
Li et al (1987)	-Controlled trial -treatment vs. no treatment	Women who met NDDG criteria for GDM but were normal or had IGT by WHO criteria	N=73 (no treatment) N= 85 (diet treatment)	-No differences in rates of macrosomia or cesarean sections between treated and untreated women	-Allocation to treatment was alternate and not random -Small sample size

Coustan and Lewis (1978)	-Randomized trial -diet treatment vs. diet and insulin treatment vs. no treatment	Carpenter & Coustan criteria	N=27 (diet and insulin) N=11 (diet alone) N=34 (no treatment)	-Macrosomia was significantly lower in the insulin and diet treated group (7%) compared with diet treated (36%) or untreated (50%) groups. -No differences in perinatal death and cesarean section rates between groups	-Incomplete randomization (28% not randomized) - No control for confounding by maternal weight
Persson et al (1985)	-Randomized trial -diet treatment vs. insulin and diet treatment	Uncommon criteria	N=105 (diet only) N=97 (diet and insulin)	-No differences between groups in prevalence of large-for-gestational age (LGA) (> 90th percentile) infants, neonatal hypoglycemia, hyperbilirubinemia and respiratory complications	-Incomplete randomization: diet treated cases with persistent hyperglycemia were treated with insulin (n=15)

Garner et al (1997)	-Randomized trial -routine obstetric care (no dietary advice) vs. intensive treatment (dietary restriction, frequent SMBG)	Uncommon criteria	N=150 (routine care) N=149 (diet treated)	-No differences between groups in mean birth weight, macrosomia, operative deliveries, birth trauma, neonatal hypoglycemia, hyperbilirubinemia	-Imperfect randomization: control women were switched to treatment arm if poor glycemic control -Women in the routine care group may have modified their diet following GDM diagnosis
Coustan and Imarah (1984)	-Observational study -insulin and diet treatment vs. diet treatment only vs. no treatment	Carpenter and Coustan criteria	N=115 (diet and insulin) N=184 (diet alone) N=146 (untreated GDM)	-Prevalence of macrosomia was significantly lower in the insulin treated group (7%) vs. diet treated group (18.5%) or untreated group (17.8%) -No significant differences in perinatal mortality or morbidity rates	-Potential selection bias -Good control for confounding for infant macrosomia

Santini & Ales (1990)	-Observational study - screenees vs. non-screenees	-NDDG criteria -Physician diagnosis	N=533 (Unscreened) N=774 (Screened)	-No differences in perinatal mortality, macrosomia, and other infant morbidity between screened vs. unscreened women but primary cesarean sections rates were significantly higher among screened women -43 of 44 (physician-diagnosed) cases of GDM were treated with diet or diet & insulin. Maternal or neonatal outcomes did not differ between treated GDM, untreated GDM or unscreened women	-Potential bias as screened women were more likely to be obese than unscreened women -Sample size too small (n=43) to determine effect of GDM treatment
Naylor et al (1996)	-Observational study -treatment vs. no treatment vs. negative screenees	-NDDG criteria (treated GDM) -Carpenter & Coustan criteria (untreated GDM)	N=115 (untreated GDM) N=143 (treated GDM) N=2940 (Negative Screenees)	-Women not treated for GDM has significantly higher rates of infant macrosomia (28.7%) compared with women treated for GDM (10.5%) or negative screenees (13.7%) -Both treated and untreated GDM cases had significantly higher rates of cesarean section compared with negative screenees	-Control for confounding unclear for macrosomia -Good control for confounding while comparing cesarean section rates

Rey et al (1996)	-Observational study -treatment vs. no treatment vs. nondiabetic controls	Varied criteria	N=120 (treated GDM) N=50 (untreated GDM) N=904 (nondiabetic controls)	-Rate of infant macrosomia (>4000 g) was significantly higher among untreated GDM women (18%) compared with treated GDM women (6.7%) or controls (6.7%) -Neonatal hypoglycemia (24% vs. 10% vs. 10%) and hyperbilirubinemia (40% vs. 21.7% vs. 22.8%) were also significantly more common among untreated GDM women compared with treated GDM women and controls respectively	-Inconsistent criteria for GDM diagnosis -High prevalence of GDM (9%) for a predominantly White sample -Potential selection bias as obesity was more common among screened than unscreened women
Adams et al (1998)	-Observational study -diet treatment vs. diet and insulin treatment vs. no treatment vs. nondiabetic controls	NDDG criteria	N=16 (untreated GDM) N=297 (diet treated GDM) N=76 (diet and insulin treated GDM) N=64 (nondiabetic controls)	-Untreated GDM cases had significantly higher rates of macrosomia (44%) compared with diet treated GDM (15%) or controls (8%) -Rates of hyperbilirubinemia, hypocalcemia, polycythemia and respiratory distress were significantly higher among untreated cases vs. controls	-Well-controlled study

Mello et al (1997)	-Observational study -diet treated GDM vs. diet and insulin treated GDM vs. negative screenees	Carpenter & Coustan criteria	N=121 (diet and insulin) N=96 (diet only) N=1052 (negative screenees)	-Diet treated GDM women had significantly higher rates of LGA infants (18.8%) compared with diet and insulin treated GDM women (9.9%) or negative screenees (8.3%)	-No control for confounding
Langer et al (1994)	-Observational study -conventional treatment (infrequent SMBG, 23% of women on insulin) vs. intensive treatment (frequent SMBG, 66% of women on insulin) vs. nondiabetic controls	NDDG criteria	N=1316 (conventional treatment) N=1145 (intensive treatment) N=4922 (nondiabetic controls)	-Significantly higher rates of infant macrosomia in conventional treatment group (13.6%) vs. intensive treatment group (7.1%) or controls (8.1%) -Rates of cesarean section, neonatal metabolic complications, stillbirth, shoulder dystocia, respiratory problems and intensive care admissions in the intensive treatment group were lower than the conventional treatment group but similar to controls	-Poor generalizability: Study women predominantly Mexican American -Well controlled study

2.2 Infant Macrosomia

This section reviews the current literature on risk factors for infant macrosomia. Given the wide array of factors that can influence fetal growth (Kramer 1987a), this review will be limited to a discussion of specific risk factors for infant macrosomia that formed the premise of this doctoral work, i.e. non-modifiable risk factors including maternal age, parity, height, ethnicity and infant gender and modifiable risk factors including maternal pregravid weight, gestational weight gain, post-term delivery, glycemic status and smoking status.

2.2.1 Definition

Birth weight is a critical determinant of perinatal morbidity and mortality and is determined by the rate of fetal growth and the duration of gestation (Institute of Medicine 1990). The relationship between birth weight and neonatal mortality is U-shaped. Infant mortality increases sharply with birth weights <2500 or >4250 g; the lowest rate occurring between birth weights of 3500-4000 g (Chase 1969, Saugstad 1981). Macrosomia is a term used to refer to large fetuses. The definition of infant macrosomia varies widely in the literature, the most common ones being birth weight >4000 g (Boyd et al 1983, Kolderup et al 1997, Meshari et al 1990), >4500 g (Spellacy et al 1985, Wilkstrom et al 1988) or birth weight >90th percentile for gestational age of a reference population (Jacobson et al 1989, Miller et al 1988). The reported prevalence of macrosomia by each of these definitions is 10-32% (Boyd et al 1983, Elliot et al 1982, Gregory et al 1998), 0.5-1.4% (Gonen et al 1996, Boyd et al 1983) and 8-14% (Kitzmiller 1986, Hediger et al 1998) respectively.

2.2.2 Predictors of Infant Macrosomia

a) Non-Modifiable Predictors

i. Age

Extremes of maternal age (≤16 y or ≥35 y) are associated with suboptimal pregnancy outcomes (Kramer 1987a, Prysak et al 1995). While both extremes in age increase the risk for low birth weight, only advanced maternal age increases the risk for high birth weight. Cogswell and Yip (1995) reported that teenage mothers gave birth to

lighter babies on an average (-149 g for Caucasians and -99 g for blacks), whereas women ≥35 y of age gave birth to heavier infants (+ 50 g for both races) compared with women aged 20-34 y. In a study of 348 black women, Essel and Opai-Tetteh (1995), found that older maternal age (30-39 y) was more common among macrosomic infants (>4000 g) vs. control infants (3000-3200 g) (33.9% vs. 17.8%, $p<0.01$). Similarly, Spellacy et al (1985) reported a higher mean maternal age among infants with mild (4500-4999 g) or severe macrosomia (>5000 g) compared with control infants (2500-3499 g) (28.6 ± 5.5 y or 29.1 ± 5.6 y vs. 25.8 ± 5.7 y, respectively; $p<0.05$). Whether maternal age had an independent effect on infant birth weight in these studies is questionable, however, as potential factors confounding this relationship such as parity and maternal anthropometry were not controlled. Studies which have controlled for confounders adequately are not consistent with regard to the effect of maternal age on the risk for macrosomia. While some studies report an increased risk for macrosomia with advancing age independently of other factors (Larsen et al 1990), others report no significant effect (Scott et al 1982, Johnson et al 1992). These inconsistent findings may in part be due to the different age intervals used in the analyses across studies. While Larsen et al (1990) determined the effect of age by 5 y intervals from 15-30 y, Johnson et al (1992) categorized age as <20 y, 20-26 y and >26 y and Scott et al (1982) evaluated the effect per standard deviation increase in maternal age.

ii. Ethnicity

Differences in mean birth weight have been noted among different ethnic groups world-wide, ranging from 2400 g among the Lumi of New Guinea to 3830 g among the Cheyenne in the United States (Meredith 1970). In North America, Caucasian infants have a higher mean birth weight compared with African-American (Cogswell and Yip 1995) or Chinese infants (Wen et al 1995) born in the United States or Canada, even after accounting for differences in maternal demographic and anthropometric factors.

Ethnic differences in birth weight may represent both genetic and environmental influences, but the relative effects of the two factors are still unclear. The effect of maternal ethnicity on infant birth weight has been mainly studied with the objective of identifying risk factors for low birth weight or infant mortality (Kramer 1987a, Kleinman

1991). There is little published information regarding ethnic differences in macrosomia prevalence. In a study of 14,219 births in West Jerusalem, infants of North African origin had higher mean birth weight compared with infants of other ethnic groups after accounting for the effects of gestational age, infant gender, parity, maternal smoking and body mass (Yudkin et al 1983). Similar findings were reported in a study (Buekens et al 1995a) comparing mean birth weight of Belgian infants with immigrant North African infants. In the latter study, North African infants had higher mean birth weight, despite their lower socio-economic status, and their entire birth weight distribution was shifted to the right compared with Belgian infants. The prevalence of macrosomia was not reported. Wasse et al (1994) reported that infants of first-generation Ethiopian women in the United States were more likely to deliver macrosomic infants (≥4000 g) than US-born blacks (20% vs. 4%) and this was not due to differences in gestational age, gestational diabetes or parity. The risk remained elevated after adjusting for maternal age, smoking, and marital status (RR: 4.0, 95% CI: 2.3-6.8). Although gestational diabetes was more common among Ethiopian women compared with US Blacks, this factor was not adjusted for in the analyses. Also, no information on maternal body weight or height was available (Wasse et al 1994). A high prevalence of macrosomia (birth weight >4000 g) has also been reported among many North American Native groups (Thomson 1990, Murphy et al 1993, Dyck and Tan 1995, Caulfield et al 1998) compared with the general US or Canadian population, but the reasons for these ethnic differences have not been explored.

In conclusion, ethnic differences in mean birth weight and infant macrosomia prevalence may either reflect differences in genetic traits or differences in gestational duration, maternal anthropometry, socio-economic status, diet or lifestyle. Differences in maternal characteristics between ethnic groups need to be precisely measured and accounted for before attributing ethnic differences in birth weight to genetic differences.

iii. Parity

Multiparous women are 2–3 times more likely to deliver macrosomic babies (>4000 g) compared with primiparous women (Modanlou et al 1980, Essel and Opai-Tetteh 1995). Grand multiparity (≥5 births) may further increase the risk (Toohey et al 1995). It is important to separate the effects of parity from age and body weight because

multiparous women tend to be older and heavier compared with primiparous women (Brown et al 1992). However, some studies have shown that multiparous women deliver bigger babies independently of age and pregravid weight (Larsen et al 1990, Johnson et al 1992). The mechanism by which multiparity independently increases fetal growth is not understood (Cogswell and Yip 1995).

iv. Height

The effect of maternal height on fetal growth may reflect genetic potential for growth or uterine capacity for fetal growth (Kramer 1987a, Cogswell and Yip 1995). Taller women have bigger babies and the effect is independent of the effect of maternal weight (Cogswell and Yip 1995). The risk for infant macrosomia increased 2-3 fold among tall women (>162.5 cm or >167 cm) compared with short women (≤155 or 157 cm) in two well-controlled studies (Larsen et al 1990, Johnson et al 1992)

v. Infant sex

Male infants tend to be heavier than female infants on an average. Based on a meta-analysis of 15 studies from developed countries, Kramer (1987a) reported that male infants were 126.4 g heavier than female infants. A majority of macrosomic infants (60-70%) also tend to be male (Lazer et al 1986, Spellacy et al 1985).

b) Modifiable Predictors

i. Prepregnancy weight

The association of maternal prepregnancy body weight with infant size may reflect genetic inheritance of body size or composition and/or availability of maternal fuel reserves at the start of pregnancy (Kramer 1987a, Cogswell and Yip 1995). Over the past two decades, there has been a trend towards increasing overweight among women of childbearing age and also an increase in the prevalence of macrosomic infants. Data from 22 states in the US indicate that the prevalence of pre-pregnancy obesity (BMI >29 kg/m^2) increased from 19.4% in 1979 to 32.6% in 1993 (Perry et al 1995a). The proportion of macrosomic infants also increased in the US from 8.2% in 1965 (National Center for Health Statistics 1988) to 11.3% in 1986-87 (Buekens et al 1995b).

The relationship between maternal pregravid body mass and infant birth weight has been described as linear (Abrams and Laros 1986). Measures of pregravid weight are either based on maternal recall (Yu and Nagey 1992) or the first available weight during early pregnancy (Institute of Medicine 1990). Methodological problems associated with recalled weight include underestimation of pregravid weight by overweight women and overestimation by underweight women (Perry et al 1995b, Stevens-Simon et al 1992). Also, pregravid weight based on early gestational weight may include some amount of early gestational weight gain or loss. However, these errors are unlikely to bias the effect on infant birth weight, as these measures are recorded before the birth of the infant (Cogswell and Yip 1995). Pregravid obesity has been variably defined in the literature based on cut-offs of absolute prepregnancy weight (Johnson et al 1992, Perlow et al 1992), prepregnancy weight as a percent of ideal body weight (Mitchell and Lerner 1989, Naeye 1990, Larsen et al 1990, Wen et al 1990) or BMI (Larsen et al 1990, Johnson et al 1992, Institute of Medicine 1990).

Maternal pregravid obesity has been found to independently increase the risk for infant macrosomia in most studies. In a study among 3191 low income women, Johnson et al (1992) found a significantly elevated risk for infant macrosomia among women in the highest quartile of prepregnancy weight (>155 lb) (Odds ratio: 3.6, 95% CI: 2.6-4.8) but not among those in the highest quartile of BMI (>29 kg/m^2), compared with women in the lowest quartiles of weight ($\leq$116 lb) or BMI (<19.8 kg/m^2), after adjusting for the effects of maternal height, net weight gain, ethnicity, diabetes, gestational age at delivery, infant gender and demographic variables. Larsen et al (1990) found a two-fold higher risk for macrosomia among obese women (pregravid BMI >32.3 kg/m^2) compared with normal weight women (BMI $\geq$20.0 to 24.9 kg/m^2) (Odds ratio: 2.2, 95% CI: 2.0-2.3) enrolled in the Women, Infant and Children (WIC) program in the United States, after adjusting for maternal height, ethnicity, age, parity, gestational duration and infant sex. The effect of gestational weight gain was not adjusted in this analyses, which may underestimate the effect of pregravid weight on birth weight, as obese women generally gain less weight during pregnancy (Cooper et al 1995, Siega-Riz et al 1994). Abrams et al (1986) studied the effect of pregravid body weight on birth weight among 2946 women from a broad socio-economic base. Very overweight women (>135% of ideal body

weight) delivered infants who weighed 179 g more on average compared with infants of normal weight women (90-120% of ideal body weight). Unfortunately, neither the prevalence nor the risk for infant macrosomia associated with pregravid weight was determined in this study. In an analysis of 60,077 singleton term births, Cogswell and Yip (1995) reported that mean birthweight was 150 g higher among infants of obese mothers (BMI >29 kg/m^2) compared with infants born to women with normal prepregnancy BMI (19.8-26 kg/m^2). Scott et al (1982) reported that 26% of the risk for infant macrosomia in their study could be attributed to prepregnancy weight after accounting for the effects of parity, smoking status, height, pregnancy weight gain, previous live births and maternal age.

In addition to total body obesity, central obesity has been recently identified as a risk factor for high birth weight. Central fat distribution is associated with higher levels of fatty acids, circulating triglycerides, hormonal changes, increased fasting glucose levels and insulin resistance, all of which can potentially influence fetal weight (Brown et al 1996). Waist-to-hip ratio and waist circumference are commonly used as indicators of central obesity. However, uncertainty exists regarding the gestational age up to which these measures would accurately reflect central adiposity without including the increase in uterine growth as pregnancy progresses (Branchtein et al 1997). Results of one study indicate that waist-hip ratio could be used as an indicator of central adiposity until 26 weeks of gestation which corresponds to a uterine height of 26 cm (Branchtein et al 1997). In the only study that evaluated the impact of central fat patterning on birth weight (Brown et al 1996), a 0.1 unit increase in waist-hip ratio (WHR) (measured 1 year before conception through 45 days post-conception) increased birth weight by 120 g, after controlling for the effects of socio-economic status, ethnicity, age, parity, BMI, height, gestational weight gain, skinfold thickness, smoking, infant sex, gestational age, and gestational diabetes. An interaction between BMI and WHR was also noted. For every 0.1 unit increase in WHR, birth weight increased by 42 g for a BMI of 20, by 162 g for a BMI of 25 and by 281 g for a BMI of 30 kg/m^2.

To summarize, the impact of maternal obesity on infant growth has been evaluated using different indices and different cut-offs across studies. The relation between the two appears to be strong and consistent even after controlling for the effects

of other confounders. The additional risk imparted by central obesity for infant macrosomia warrants further investigation.

ii. Gestational weight gain

Weight gain during pregnancy comprises an increase in various maternal tissues, plasma volume, fat stores, weight of the fetus, placenta and amniotic fluid (Hytten and Thomson 1976). The total amount, pattern and composition of weight gain are known to impact fetal growth (Institute of Medicine 1990). While inadequate pregnancy weight gain can increase the risk for fetal growth retardation (Kramer 1987a), excessive weight gain can elevate the risk for fetal macrosomia (Johnson et al 1992, Cogswell et al 1995). Total weight gain during pregnancy is calculated as the difference between weight at or before delivery and either recalled pregravid weight or the first measured weight during early pregnancy (Institute of Medicine 1990). Because total gestational weight gain includes the weight of the fetus, net weight gain (total weight gain-birth weight) rather than total weight gain should be used to prevent an overestimation of the effect of gestational weight gain on birth weight (Kleinman et al 1990). Although gestational weight gain by itself is an important determinant of fetal growth, its effect is modified by the woman's pregravid weight status. The effect of gestational weight gain on infant birth weight is strong among underweight or normal weight women and weak or insignificant among overweight or obese women (Abrams et al 1986). The amount of weight gained during pregnancy also depends on the duration of pregnancy. Therefore, in determining the impact of gestational weight gain on birth weight, weight gain should either be expressed as a rate (kg/week) or the effect of gestational age should be adjusted statistically in the analyses (Selvin and Abrams 1996). Other potential confounders that need to be considered are race, socioeconomic status and smoking status (Kramer 1987a).

Given the high variability of weight gain among women with healthy pregnancy outcomes and the interaction of weight gain with pregravid weight, the Institute of Medicine (1990) of the United States proposed ranges rather than single values for pregnancy weight gain, specific to BMI. The recommendations for weight gain stratified by pregravid BMI are as follows: 28-40 lb for underweight women (BMI <19.8 kg/m^2), 25-35 lb for normal weight women (BMI ≥ 19.8-26 kg/m^2), 15-25 lb for overweight

women (BMI >26-29 kg/m^2) and a minimum of 15 lb for obese women (BMI >29 kg/m^2). These recommendations are more liberal than those recommended previously owing to the Institute of Medicine (1990) committee's view that restricted fetal growth constituted a more important public health problem than macrosomia. This has been recently criticized by Johnson and Yancey (1996) and Feig and Naylor (1998) who question the methodologic adequacy of studies on which these recommendations were based. The latter authors also caution that the Institute of Medicine's liberal recommendations may lead to excessive weight gains and associated problems of infant macrosomia, operative deliveries, post-partum weight retention, obesity, and diabetes. Various studies conducted in the United States, following the publication of the guidelines, indicate that only 30-40% of pregnant women gain weight within the recommended ranges (Abrams 1994). In two recent studies, the risk for infant macrosomia was 2-4 fold higher among women whose pregnancy weight gain exceeded the Institute of Medicine recommendations compared with those whose weight gains were in accordance with the Institute of Medicine guidelines. A weight gain >25 lb was defined as excessive for obese women in these studies (Cogswell et al 1995, Caramichael et al 1997).

Pregnancy weight gain tends to be more variable among obese women compared with underweight or normal weight women (Abrams and Laros 1986, Kleinman 1990). Few studies have evaluated effects of gestational weight gain on birth weight among obese women (Abrams and Laros 1986, Kleinman 1990). Given the paucity of information, the Institute of Medicine (1990) recommended that obese women (BMI >29 kg/m^2) gain a minimum of 15 lb, which corresponds to the weight of the fetal compartments (fetus, placenta and amniotic fluid), but did not specify an upper limit. Some studies since the Institute of Medicine report, have attempted to identify an upper limit for pregnancy weight gain among obese women. Cogswell et al (1995) found that among obese women (BMI >29 kg/m^2), the risk for infant macrosomia increased by 30% with weight gains of 25-29 lb and doubled with weight gains of ≥30 lb compared with weight gains between 15-19 lb. These authors recommended an upper threshold of 25 lb for weight gain among obese women, as higher gains increased the risk for macrosomia without reducing the likelihood for low birth weight. In another study (Parker and

Abrams 1992), the risk for growth-retarded infants (<10th percentile for gestational age) was not reduced but the risk for macrosomic infants increased by 40% among obese women (BMI >29 kg/m^2) who gained >37 lb compared with those who gained between 20-37 lb. Similarly, Bianco et al (1998) reported that weight gain or loss among morbidly obese women (BMI >35 kg/m^2) did not influence the risk for growth retardation, whereas a weight gain of >25 lb significantly increased the risk for infant macrosomia. These studies indicate the need to limit weight gain among obese women to minimize the risk for infant macrosomia.

The pattern and composition of gestational weight gain may also have important implications for fetal growth. However, there are few published studies which have evaluated the optimal pattern of maternal weight gain during pregnancy or its relationship with fetal growth. Among women with good pregnancy outcomes, i.e. delivery of a live-born infant with birth weight between 3-4 kg at 39-41 weeks gestation, weight gains in the second and third trimester were higher among underweight or normal weight women than among overweight or obese women (Caramichael et al 1997). In a study among pregnant adolescents (Scholl et al 1990), gestational weight gain <25th percentile at 16 weeks was associated with an increased risk for low birth weight whereas weight gain >75th percentile during the same period significantly increased the risk for infant macrosomia (adjusted Odds ratio: 2.3, 95% CI: 1.3-4.1). Muscati et al (1996) reported that high early gestational weight gain (up to week 20) did not decrease the proportion of small-for-gestational age infants, increased the risk for large-for-gestational age infants and resulted in greater post-partum weight retention among healthy non-smoking women. These studies suggest that the best pattern of weight gain would be one that paralleled the period of rapid fetal growth, i.e. the second half of pregnancy. Besides the timing of gestational weight gain, the composition of the weight gained during pregnancy can also influence fetal growth. Several studies have reported no correlation between maternal fat accretion during pregnancy and infant birth weight among well nourished women (Langhoff-Roos et al 1987, Lawrence et al 1991) but significant associations among undernourished women (Villar et al 1992, Viegas et al 1987).

In conclusion, the existing evidence suggests that there may be a threshold effect of gestational weight gain on fetal growth, which varies by maternal pregravid weight

status. Excessive pregnancy weight gain (especially during the first half of gestation) is of concern because of the increased risk for infant macrosomia but intervening early enough in pregnancy to control early gestational weight gain is difficult.

iii. Glycemic status

In this section, the literature on macrosomia prevalence among women with gestational diabetes mellitus (GDM) or lesser degrees of glucose intolerance vs. normoglycemic women will be reviewed. The effect of pregestational diabetes on infant macrosomia will not be covered given the exclusion of pregestational diabetic women from the studies conducted as part of this doctoral research. Also, the review will be restricted to studies which have adequately controlled for confounding.

Pedersen's hypothesis is commonly used to explain the effect of maternal glycemic levels on infant size, i.e. maternal hyperglycemia primes the fetal pancreas to secrete excessive amounts of insulin, resulting in increased fetal growth and adiposity due to the anabolic effects of this hormone (Pedersen and Osler 1961). Although GDM may potentially cause infant macrosomia through this mechanism, the importance of GDM as a risk factor for macrosomia is under debate (Okun et al 1997b, Maresh et al 1989) because the effect of GDM has not been clearly distinguished from that of maternal obesity, which is an important risk factor for both GDM and infant macrosomia.

The reported prevalence of infant macrosomia (>4000 g or >90th percentile) among women with GDM ranges from 10% to 35% (Langer et al 1989, Hod et al 1991, Casey et al 1997), depending on the criteria used for diagnosing GDM, treatment for GDM and presence of other risk factors. Several well-controlled studies comparing rates of infant macrosomia between women with GDM and normoglycemic controls report equivocal findings. Jang et al (1997) compared macrosomia prevalence between 65 women with GDM and 153 normoglycemic controls matched for age, height and pregravid weight. Infants of women with GDM weighed 138 g more and had a higher prevalence of macrosomia (>4000 g) (13.8% vs. 3.3%, $p<0.01$) compared with control infants. Di Cianni et al (1996) found a higher prevalence of infant macrosomia (>4000 g) among normal weight (BMI <25 kg/m^2), overweight (25-30 kg/m^2) and obese (BMI >30 kg/m^2) women with GDM compared with normoglycemic women in similar BMI

categories (41.5 %, 57.4% and 76.9% vs. 6.8%, 10.2% and 25.9% respectively, $p<0.01$). Casey et al (1997) matched women with class A1 GDM (fasting plasma glucose <5.8 mmol/L) (n=874) with non-diabetic controls (n=1748) for age, parity, ethnicity and pregravid weight. Rates of infant macrosomia (>90th percentile) were significantly higher among women with GDM compared with controls (35% vs. 23%) and the risk attributable to GDM alone was determined to be 12%.

In contrast to these studies, Okun et al (1997b) compared 209 macrosomic infants with 791 non-macrosomic infants and found that treated GDM was not a significant risk factor for infant macrosomia (≥4000 g), whereas maternal obesity was a strong risk factor after controlling for ethnicity, age, parity, weight gain, infant gender, maternal birth weight, height and smoking status. The risk for macrosomia increased 1.5 times for every 15 kg increase in pregravid weight. Adams et al (1998) compared macrosomia rates (>4000 g) between women not treated for GDM (n=16), women treated for GDM with diet (n=297) and normoglycemic controls (n=64) and found similar rates of infant macrosomia among treated cases (9%) and normoglycemic controls (5%) but significantly higher rates among untreated cases of GDM (44%) ($p<0.0005$), after controlling for the effects of age, ethnicity, parity, BMI, pregnancy weight gain, and gestational age at delivery. Maresh et al (1989) did not find an increased prevalence of macrosomia (>90th percentile) among diet-treated (14%) or diet- and insulin-treated (19%) women with GDM compared with non-diabetic controls (10%). However, macrosomia prevalence was significantly higher among obese (BMI ≥31 kg/m^2) vs. non-obese women (24% vs. 10%, $p<0.01$) after adjusting for the effects of age, gestational age and severity of GDM. Differences in the effect of glycemic level on infant macrosomia among women treated for GDM across studies are likely due to differences in the degree of hyperglycemia, treatment modality, or duration of treatment.

Other studies indicate that even milder degrees of glucose impairment may be associated with an increased risk for macrosomia among presumably normoglycemic women who do not meet the criteria for GDM. Sermer et al (1995) found that the risk for infant macrosomia (>4000 g) increased with increasing fasting plasma glucose values on the oral glucose tolerance test, after adjusting for age, ethnicity, parity, height and body mass index. For every 1 mmol/L increase in fasting plasma glucose, the odds for

macrosomia increased by 100%. Tallarigo et al (1986) reported a significant increase in macrosomia (>4000 g) with increasing 2-h plasma glucose values on the 100 g OGTT. Others report a higher prevalence of macrosomia among women with a positive screen but negative OGTT (Leikin et al 1987) or those with one abnormal value on the OGTT (Lindsay et al 1989) compared with those with normal screen or normal OGTT values at all time points after adjusting for the effect of body weight.

In conclusion, a majority of well-controlled studies indicate that maternal glycemic levels significantly increase the risk for infant macrosomia even after accounting for the effects of other factors known to impact birth weight. However, the relationship between maternal glycemic levels and fetal growth appears to be linear without a clear glycemic limit above which the risk for fetal macrosomia increases.

iv. Cigarette smoking

Maternal smoking during pregnancy has a negative impact on birth weight and can shift the entire birth weight distribution to the left (Cogswell and Yip 1995). Therefore smokers are less likely to deliver macrosomic infants. Although smoking is protective of macrosomia and is modifiable, it obviously should not be used in that way, given its multiple negative effects on maternal and infant health. The mechanism by which smoking retards fetal growth is not well understood. The effect may be mediated through poor maternal nutrition, inadequate weight gain or through direct metabolic disturbances such as decreased availability of oxygen and nutrients to the fetus, vasoconstriction and placental insufficiency (Harrison et al 1983, Haste et al 1991).

Maternal smoking can independently decrease mean birth weight by 150 g or 11.1 g/cigarette smoked/day (Kramer 1987a). A dose-response relationship has been described between maternal smoking during pregnancy and fetal growth, with increased smoking significantly decreasing infant weight, length and head circumference (Hebel et al 1988, Britton et al 1993, Abel et al 1980, Secker-Walker et al 1997). The adverse effects of maternal smoking on fetal growth can be eliminated or minimized if women quit smoking before pregnancy or early in pregnancy. The improvement in birth weight due to smoking cessation during pregnancy may range from 90-217 g (Olsen 1992, Mainnous and Hueston 1994, Frank et al 1994). One study reported a higher mean birth weight

(3548 g vs. 3258 g, $p<0.0001$) and risk for infant macrosomia (>4000 g) (RR: 3.1, 95% CI: 1.2-8.0) among women who quit smoking by 28 weeks gestation compared with nonquitters, and the effect was observed to be independent of gestational weight gain (Mongoven et al 1996). However, it is not clear whether the effect of pregravid weight was taken into account in this analysis.

Factors that can confound the association between smoking and birth weight are maternal age, parity, ethnicity, socio-economic status, psychological stress, and alcohol intake (Kramer 1987a), and the reported effects of smoking on birth weight across studies depends on which of these factors were controlled in the analyses. Maternal factors that could modify the effect of smoking on birth weight are maternal age and pregravid weight. Smoking decreases birth weight to a greater extent among older women compared with younger women. Several studies (Wen et al 1990, Fox et al 1994) report a decrease in birth weight by 301-376 g among older women (>35 or 40 y) compared with a decrease of 117-134 g among younger women (<16 or 17 y). Effect modification of smoking by pregravid weight is controversial. While some studies report that maternal overweight may protect the fetus against the growth-retarding effects of smoking (Garn et al 1979), others report similar degrees of growth retardation among infants of underweight, normal weight or overweight smokers (Haworth et al 1980, Hellerstedt et al 1997).

In conclusion, smoking appears to have a strong negative impact on fetal growth, which varies with the number of cigarettes smoked, duration of smoking and stage of gestation. In determining the effect of cigarette smoking on infant birth weight, the confounding or interactive effects of other risk factors need to be studied simultaneously.

v. Gestational age

Gestational age or the duration of pregnancy is one of the most important determinants of fetal size (Kramer 1987b). Estimates of gestational age are based either on the recalled last normal menstrual period (LNMP) or ultra-sound dating. In cases of irregular menstruation or unavailability of gestational age estimates by LNMP or ultra-sound dating, gestational age may be estimated from a clinical assessment of the infant at birth but this method is fraught with errors (Shukla et al 1987, Andersen et al 1981). Date

of confinement based on LNMP can also result in significant misclassification of preterm or post-term gestations compared with ultra-sound dating done between 16-20 weeks gestation (Kramer et al 1988, Henriksen et al 1995). Post-term pregnancy (≥42 weeks) is an important predictor of infant macrosomia. In several well-controlled studies, a 1.5-2 fold increase in risk for infant macrosomia was reported for post-term pregnancies (≥42 weeks) compared with term pregnancies (37-41 weeks) (Larsen et al 1990, Johnson et al 1992).

2.3 The Epidemiology of Gestational Diabetes Mellitus and Infant Macrosomia among North American Native Populations

2.3.1 Gestational diabetes mellitus (GDM) among North American Natives

Since the 1940s, a dramatic increase in diabetes prevalence rates has been reported among various Native peoples in North America (Young 1988). Prior to 1940, diabetes among North American Native people was reportedly very rare. This may have been due to infrequent screening or testing for diabetes before 1940 or a genuine paucity of diabetes cases, as indicated by some reports based on urinary glucose testing among some Native groups (West 1974). The "dramatic" increase in diabetes among Native peoples has been attributed to "acculturation" to a more western lifestyle, with associated changes in dietary and physical activity patterns. Indeed, increased prevalence rates of some chronic diseases following acculturation have been reported for Aboriginal populations throughout the world (Daniel and Gamble 1995).

The "thrifty gene" hypothesis first proposed by Neel (1962) has been commonly used to explain the high rates of diabetes among Aboriginal populations. According to this hypothesis, the thrifty gene conferred survival advantage in the harsh environment of primitive peoples through a 'quick insulin trigger'. This mechanism allowed for more efficient conversion and storage of food energy as fat during "feast periods," providing an energy reserve during times of food scarcity. However, this thrifty mechanism is not suited for the modern lifestyle of Aboriginal peoples, which is characterized by high energy intake and physical inactivity, leading to hyperinsulinemia, obesity and diabetes (Neel 1962). Several criticisms have been directed against this hypothesis. Szathmary (1987) contends that a 'quick insulin trigger' would not be thrifty for Aboriginal people in the arctic and subarctic environment, whose traditional diets were almost devoid of carbohydrate. A thrifty mechanism in this environment would be one that enhanced glucose production such as gluconeogenesis, to meet the needs of the glucose-dependent organs. Another argument against Neel's hypothesis is that a 'quick insulin trigger' would be beneficial only in the presence of increased insulin sensitivity. However, insulin resistance appears to be the major

metabolic defect in Type 2 diabetes (Reaven 1998). Cahill and Wen (1967) propose selective insulin resistance in the muscle as an alternative mechanism that could provide survival advantage. This mechanism would spare glucose for use by the central nervous system, allow for efficient fat storage during feast periods and minimize muscle proteolysis (for gluconeogenesis) during starvation through the use of ketone bodies as fuel from fat breakdown. Hales and Barker (1992) suggest that low birth weight due to undernutrition in the intrauterine environment can adversely affect the fetal pancreas leading to Type 2 diabetes subsequently, when further stressed by factors such as obesity. An alternative explanation suggested by McCance et al (1994) is that low birth weight infants who survive are those who are more likely to be genetically predisposed to insulin resistance and diabetes. All these hypotheses have a common element in that they indicate some metabolic alteration that favors survival in undernutrition but is detrimental under improved nutritional conditions (Ozanne and Hales 1998). However, the thrifty mechanism and the metabolic processes affected remain under dispute.

Published information on the prevalence of GDM among different Native Nations in North America is limited; the available information is summarized in Table 1. The reported prevalence of GDM ranges from 1.6% among the Pima Indians of Arizona to 14.3% among the Zuni Indians of western New Mexico. However, these prevalence figures may be an underestimate due to incomplete screening and/or diagnosis.

Table 1. GDM Prevalence among North American Natives

Native Group	Sample Size	GDM Criteria	GDM Prevalence (95% CI)
Zuni Indians *(Benjamin et al 1993)*	N = 809 (1987-1990)	NDDG	14.3% (11.8-16.8)
Cree and Ojibwa *(Harris et al 1997)*	N=1263 (1990-1993)	NDDG	8.7% (6.9-10.6)
Dene & Cree (*Dyck et al 1995*)	N= ? (1991-1992)	self-reported	8.2%
Yup'ik Eskimos (*Murphy et al 1993*)	N=605 (1984-1988)	NDDG	5.8% (3.9-7.7)
Chippewa (*Rith-Najarian et al 1996*)	N=548 (1990-1992)	NDDG	5.8% (1.7-9.9)
Navajo Indians (*Sugarman et al 1989*)	N=4094 (1983-1987)	NDDG	4.3% (3.7-4.9)
Tohono O'odham (*Livingston et al 1993*)	N=1854 (1987-1988)	NDDG	3.2% (2.4-3.9)
Pima Indians (*Pettitt et al 1994*)	N=127 (1992)	NDDG	1.6% (0-7.9)

Predictors of GDM among Native peoples have not been adequately investigated. Of the studies mentioned in Table 1, only 3 evaluated risk factors for GDM (Murphy et al 1993, Rith-Najarian et al 1996, Harris et al 1997). Murphy et al (1993) reported that Yup'ik Eskimo

women with GDM were significantly older and more parous compared to negative screenees. Body mass index (BMI) was not reported in this study. In contrast, Rith-Najarian et al (1996) did not observe statistical differences in age, parity or BMI between women with and without GDM in their cohort of Chippewa women. The independence or magnitude of effect of each risk factor was not evaluated in either of these studies. In the only well-controlled study in a Native population (Harris et al 1997), age, parity, pregravid weight, family history of diabetes, and previous GDM were identified as independent risk factors for GDM among Cree and Ojibway women of northwestern Ontario, Canada. The risk for GDM more than doubled for every 5 year increase in age, 3-unit increase in BMI (until a BMI of 30), parity ≥ 1, family history of diabetes or previous GDM.

2.3.2 Infant Macrosomia among North American Natives

Infant macrosomia, rather than low birth weight, seems to be high among many North American Native groups, despite their lower socio-economic status. Their low birth weight (<2500 g) prevalence of 2.5-5.8% (Munroe et al 1984, Thomson 1990, Armstrong et al 1998) is similar to that reported for the general North American population (5.9%) (Joseph and Kramer 1997). As summarized in Table 2, studies among North American Natives report a macrosomia prevalence (>4000 g) ranging from 14.3% to 36.1% (Munroe et al 1984, Thomson 1990, Dyck and Tan 1995, Caulfield et al 1998, Armstrong et al 1998).

Table 2: Prevalence and Predictors of Infant Macrosomia among North American Natives

Native Group	Sample Size	Inclusion Criteria	Macrosomia Definition	Macrosomia (%)
Cree and Ojibway (*Munroe et al 1984*)	N=1487 (1974-1977)	None given	4001-4500 g	14.3
British Columbia Natives (*Thomson 1990*)	N=4724 (1982-1986)	Singleton live births	≥4000 g	15.9
Saskatchewan Natives (*Dyck & Tan 1995*)	N=10,709 (1975-1988)	Live births	>4000 g	16.3
Cree and Ojibwa (*Caulfield et al 1998*)	N=741 (1990-1993)	Singleton births	>4000 g	29.2
James Bay Cree (*Armstrong et al 1998*)	N=2881 (1985-1995)	Singleton live births	≥4000 g	36.1

High rates of macrosomia reported among Native North Americans might be a recent phenomenon. However, existing studies do not uniformly reveal a temporal trend in high birth weight. Data from a national survey of infant feeding practices indicate that only 12.2% of Native Canadians weighed >4000 g at birth in 1962 vs. 21.6% in 1983 (Health and Welfare Canada 1990). A comparison of all live births from 1975-1988 between northern Saskatchewan (66% aboriginal people) and southern Saskatchewan (15% aboriginal people) revealed that the yearly percentage of macrosomia increased from 12.6% to 19.2% (53% relative increase) in the North and 10.2 to 12.8% (25% relative increase) in the South over the study period (Dyck and Tan 1995). In contrast, no temporal tend in average birth weight was noted from 1968-69 to 1974-77 among Natives of the Sioux Lookout Zone (Munroe et al 1984), nor from 1985 to 1995 among the James Bay Cree (Armstrong et al 1998).

Risk factors for infant macrosomia have not been extensively investigated in Native

populations. With the exception of one study among the Cree and Ojibwa of northwestern Ontario (Caulfield et al 1998), none of the other studies on Native peoples determined independent predictors of macrosomia in well-controlled analyses. In the latter study among the Cree and Ojibway (Caulfield et al 1998), which reported one of the highest prevalence of infant macrosomia (29.2%), maternal factors which independently increased the risk for macrosomia were pregravid BMI, height, gestational weight gain, glycemic status before and during pregnancy and pyelonephritis. The risk for macrosomia attributable to maternal diabetes was 10%, whereas 25% of the risk was attributable to pregravid overweight alone (BMI >29 kg/m^2).

In conclusion, the available information on risk factors for GDM and infant macrosomia among Native populations (who have a high prevalence of both outcomes) is scarce. A majority of published studies dealing with Native groups lack adequate control for confounding and none include a comparative group of non-Native women. These drawbacks need to be addressed in future studies to advance our understanding of ethnic differences in risk for GDM and infant macrosomia.

2.4 Overall Conclusion

The preceding review summarized and critiqued contemporary findings in the literature related to prevalence and determinants of GDM and macrosomia in the general North American population and among North American Aboriginal populations. Few studies in both populations have examined independent or interactive effects of predictors of GDM and macrosomia. Also, no studies have examined the risk for GDM imparted by such modifiable factors as diet, physical activity and weight gain before GDM diagnosis. High rates of GDM and macrosomia have been reported among North American Aboriginal populations but none have used a comparative group of non-Aboriginal controls in estimating ethnic differences in risk for these outcomes. There is a clear need to investigate these issues and the studies described in the next three chapters were designed to address these questions with good study designs and rigorous methodology.

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CHAPTER 3

PREVALENCE OF GESTATIONAL DIABETES MELLITUS AMONG JAMES BAY CREE WOMEN IN NORTHERN QUEBEC

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3.1 Abstract

Background: The prevalence of gestational diabetes mellitus (GDM) has been reported to vary widely in Aboriginal populations. Most of the data have come from the United States. To help determine the extent of GDM in Canada's Aboriginal population, the prevalence was assessed in a population of Cree women in northern Quebec.

Methods: A cross-sectional study was conducted using the National Diabetes Data Group (NDDG) criteria. Information was obtained from patient charts on pregnancies between January 1995 and December 1996 among women residing in 9 communities in the eastern James Bay region of northern Quebec. Women who were non-Cree, had pre-existing diabetes, had spontaneous abortion, or were receiving glucocorticoid treatment were excluded.

Results: Data on 654 pregnancies that met the inclusion criteria were available. Results of the screening oral glucose challenge test were available for 579 of the pregnancies; the remaining 75 pregnancies were excluded. The mean gestational age at screening was 28.3 ± 2.6 weeks. The prevalence of GDM among the Cree was 12.8% (74/579) (95% CI: 10.1-15.5). The prevalence in the inland communities was twice as high as that in the coastal communities (18.0% vs. 9.3%, p=0.002). Women with GDM or impaired glucose tolerance were older, more parous, overweight and delivered heavier babies compared with their normoglycemic counterparts.

Interpretation: The prevalence of GDM among the James Bay Cree is twice as high as the general North American population and the second highest reported for an aboriginal group worldwide. Given the likelihood that a high proportion of these women may progress to Type 2 diabetes eventually, strategies for GDM and Type 2 diabetes prevention and treatment in this population need to be formulated.

3.2 Introduction

Gestational diabetes mellitus (GDM) has been defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" (1). GDM not only increases the risk for infant macrosomia (birth weight >4000), hypoglycemia, birth trauma, and cesarean sections (2) but also the risk for subsequent Type 2 diabetes in the mother (3) and her offspring (4). Despite this, there is no consensus regarding universality, method, criteria or clinical utility for GDM screening and diagnosis (5-6). While the Society of Obstetricians and Gynecologists of Canada (7) recommend universal screening for GDM between 24-28 weeks gestation, the American Diabetes Association (8), American College of Obstetricians and Gynecologists (9) and Canadian Task Force on the Periodic Health Examination (10) recommend selective screening based on the presence of certain historical or clinical risk factors.

Studies from the United States indicate that the prevalence of GDM varies widely, from a low of 3.2% among Tohono O'odham of southern Arizona to a high of 14.5% among the Zuni Indians of western New Mexico (11-16). There has been just one Canadian study which has used standardized criteria to determine GDM prevalence in a Native group (Cree and Ojibwa of northwestern Ontario) to date (17). It is important to accurately assess the prevalence of GDM in Canada's Aboriginal population to give a better understanding of the importance of the problem. Therefore, the aim of this study was to establish the prevalence of GDM among the James Bay Cree.

3.3 Methods

The Cree of James Bay belong to the Algonquian language family and subarctic culture area. Approximately 11,000 Cree people inhabit 5 coastal and 4 inland communities. The James Bay and Northern Quebec Agreement of 1975 resulted not only in relocation of various settlements but also changes in economy, health services, education, and socio-cultural traditions. Primary health care is provided by physicians and nurses at local clinics (one in each community). Most deliveries are done at Val-d'Or, Chibougamou or Chisasibi.

All births in Quebec in 1995 and 1996 to residents of the 9 communities were

identified from a birth registry maintained by the Public Health Module-Cree Region (n=637). Of these, prospective information was available for 153 pregnancies in 1995-96 and an additional 66 pregnancies in 1997, among participants in a nutrition intervention study ending in June 1997. We therefore had information for a total of 703 pregnancies in 668 different women. Women who were not Cree, had spontaneous abortions, preexisting diabetes or treated with glucocorticoids during pregnancy were excluded. The prevalence of preexisting diabetes among pregnant women was based on physician diagnosis of Type 1 or Type 2 diabetes in the woman's medical chart antedating the index pregnancy.

For all Cree women, a 1-h 50 g oral glucose challenge test (OGCT) was usually administered in the non-fasting state towards the end of the second trimester as per the recommendations of the National Diabetes Data Group (NDDG) (18). Women with a positive screen (≥ 7.8 mmol/L) are given a 3-h 100 g oral glucose tolerance test (OGTT) after an overnight fast. For women at high risk for GDM, screening may be done during the first trimester; those with a negative result undergo a repeat screening test or OGTT at about 24 weeks gestation. A fasting plasma glucose determination is also obtained during the first trimester for most women. Blood samples from women in coastal communities are generally sent to Chisasibi and from inland communities to Chibougamou for laboratory processing. Laboratory results were obtained from chart reviews of patient medical and laboratory records. GDM prevalence in this population was determined strictly by the NDDG criteria (18). In cases where a glucose meter was used for a 50 g screen, a threshold of 7.2 mmol/L for capillary blood was used instead of 7.8 mmol/L to indicate a positive screen value (19). For positive screenees with no or incomplete OGTT information, the positive predictive value of the 50 g screen was used to determine potential cases of GDM. Impaired glucose tolerance (IGT) was defined as 1 abnormal value on the 3-h 100 g OGTT (20).

Information on maternal age, pregravid weight, height, parity and infant birth weight was obtained from chart reviews. For intervention study participants, height was measured by dietitians and pregravid weights were obtained from maternal recall. For the purpose of this study, pregravid weight from maternal recall/chart review was used only if it agreed within 5 kg of pregnancy weight up to 10 weeks or 7 kg of weight at >10-14 weeks (if

available). If pregravid weight was not available, weight at the first visit (if ≤ 14 weeks) was used. Gestational age determination was based on last normal menstrual period if it coincided within 1 week of ultra-sound dating done between 16-20 weeks (21). Otherwise, ultra-sound estimates were used. Birth weights of term infants (≥37 weeks) (n=604) were used in the analysis.

The study was approved by the Cree Board of Health and Social Services of James Bay. Ethical approval was obtained from the Human Ethics Review Board of Macdonald Campus, McGill University. Informed consent was also obtained from participants in the intervention study. All statistical analyses were performed using the Statistical Analyses System (SAS, version 6.12, NC, USA). Chi-Square analysis was used to determine differences in GDM prevalence between inland and coastal communities. Student's independent t-test was used to determine differences in maternal and infant characteristics between screenees and non-screenees. Tukey's Studentized Range (HSD) test was used for multiple comparisons between women with normal, abnormal (GDM/IGT) and uncertain glycemic status (positive screenees with no/incomplete OGTT) in a one way analysis of variance. Level of significance was set at $p<0.05$.

3.4 Results

Of the 703 pregnancies during the study period, 7 files could not be located and 42 did not meet the inclusion criteria (pregestational diabetes: n=12, spontaneous abortions: n=5, non-Native status: n=22, glucocorticoid treatment: n=3). Data on 654 eligible pregnancies were thus available. The women had a median age of 23 y (range: 14.5-43 y) and 31% were nulliparous, 25% primiparous, 39% multiparous and 5% grand-multiparous (parity≥ 5). Data on pregravid weight and height were not in the charts for many women. The average pregravid body mass index (BMI) was 30.4 ± 6.7 kg/m^2 (n=275); 55.5% of the women were overweight (BMI >29 kg/m^2). The average pregravid weight was 80.9 ± 18.2 kg (n=417).

Screen values after 22 weeks gestation were available for 534 of the 654 pregnancies. Mean gestational age at screening was 28.3 ● 2.6 weeks. The median value on

the screen was 7.2 mmol/L (range: 2.9-18.5 mmol/L). Thirty seven percent (n=199/534) of the pregnancies had positive screens but only 62% of these (123/199) completed the OGTT. Of the positive screenees who completed an OGTT, 32 tested positive for GDM, yielding a positive predictive value of 26% (32/123) for the 50 g screen. 19.5% (24/123) had IGT and 54.5% (67/123) had normal glycemic status. The other 38% (76/199) high screenees either did not receive an OGTT (n=71) or had incomplete OGTT information (n=5). Reasons for no OGTT following a high screen were patient refusal or missed laboratory appointments, physician diagnosis of GDM based only on a positive screen value, missing OGTT values from patient records, or vomiting after the OGTT solution was given. We used the positive predictive value of the screen to estimate how many of these high screenees with no/incomplete OGTT information (n=76) would have tested positive for GDM had they undergone a complete OGTT. This yielded an estimate of 19.8 GDM cases (26% x 76). There were 335 pregnancies with normal screen values (<7.8 mmol/L). Of these, 18 received an OGTT based on some clinical indication. Three of the 18 pregnancies tested positive for GDM, 3 had IGT and 12 were normoglycemic. The results are summarised in Figure 1.

The remaining 120 pregnancies which were not screened by the standard protocol included 6 diagnosed with GDM during the first trimester, 33 who received a direct OGTT, 3 without screen values in their charts but they were transferred out of the community for GDM control, 3 with a capillary screen and 75 with no screen values whatsoever (Figure1). The non-screenees (n=75) were excluded from the GDM estimate, as no assumptions can be made regarding their glycemic status. Common reasons for no screen values were patient absence at laboratory appointments or no prenatal care. The final estimate of GDM prevalence over a two year period (1995-1996) among the Cree of James Bay is therefore 74/579=12.8% (95% CI: 10.1-15.5). GDM prevalence was higher in the inland (n=234) vs. coastal communities (n=345) (18% vs. 9.3% respectively, p=0.002). The prevalence of pregestational diabetes was determined to be 1.8% (12/674) (95% CI: 0.8-2.8) for the entire Native sample.

Means ± standard deviations for maternal age, parity, prepregnancy body weight and infant birth weight by screen status are presented in Table 1. Women with GDM/IGT and

those with high screens but no/incomplete OGTT were older and heavier compared with normoglycemic women. Women with GDM/IGT were also more parous and had heavier babies compared with their normoglycemic counterparts, while the values for women with high screens but no/incomplete OGTT fell between the two values. A similar trend was noted when women with IGT were pooled with normoglycemic women in the analyses. The mean age, parity, pregravid weight and infant birth weight of those screened (n=579) vs. those not screened (n=75) were very similar, indicating little risk of bias by not having values on these women (Table 1).

3.5 Conclusions

The prevalence of GDM among the James Bay Cree is 12.8%, approximately twice as high as 3-5% reported for the general North American population (22-23). In a recent Canadian study among the Cree and Ojibwa Natives of northwestern Ontario, GDM prevalence was found to be 8.7% (110/1263) using the NDDG criteria (17). Earlier Canadian surveys used self-reported data to determine GDM prevalence among some Native Canadian groups and indicated a GDM prevalence ranging from 2% in the Pacific region to 16% in Quebec (24-25). The accuracy of our estimate is enhanced by two facts. First, we had data for 88.5% of all eligible Cree women (579/654) over the study period. Second, diagnosis of GDM was made strictly in accordance with the NDDG criteria (18). Our results support other reports that women with GDM were more likely to be older, more parous, overweight (17, 26-27) and deliver heavier babies (28), compared to women without GDM. GDM prevalence was also noted to be twice as high in the inland (southern) vs. coastal (northern) communities in our study and may be indicative of lifestyle differences based on proximity to urban centres. This is supported by reports of a north-south gradient for Type 2 diabetes prevalence in the same population (29), and other Native populations (30).

Estimates of GDM among Native groups in North America using the NDDG criteria range from 3.2% among the Tohono O'odham to 14.5% among the Zuni of New Mexico (11-16). Prevalence figures reported to date, however, may be underestimated because high screenees who did not proceed to an OGTT appear to have been classified as normal. For

comparison purposes, we used the positive predictive value (PPV) of the screen, where available, to determine potential cases of GDM in each of these studies. The PPV of the 50 g screen was available for the Navajo Indians (12), Yup'ik Eskimos (13), and Chippewa (15), and ranged from 20-25%, comparable with the value of 26% obtained in our study. The use of the PPV to estimate potential cases of GDM increased the prevalence estimate from 9.3% to 12.8% among the Cree in our study (PPV=26%), 4.3% to 5.7% among the Navajo Indians (PPV=20%) (12), 5.8% to 6.6% among the Yup'ik Eskimos (PPV=22%) (13), and 5.8% to 7% among the Chippewa (PPV=25%) (15).

The prevalence of GDM among the Pima using the NDDG criteria was determined to be only 1.6% (14), but the prevalence of pregestational diabetes was 6.3% (95% CI: 3.0-9.6) (31), compared to 1.8% (95% CI: 0.8-2.8) in our study. One explanation may be more intensive screening among Pima women compared to the Cree leads to the detection of more cases of diabetes prior to pregnancy. Alternatively, because of the different genetic makeup and environmental and lifestyle factors among the Cree, infrequent pregravid diabetes may be a true phenomenon. A low prevalence of pregestational diabetes (3.2%, 95% CI: 2.3-4.2) was also noted among the Cree and Ojibwa women of Ontario, Canada (17).

A limitation of this study was that 75 women did not undergo any screening but there is no reason to believe that these women were at higher or lower risk for GDM as they were of similar age, parity and pregravid weight status. In addition, 76 women with positive screens did not undergo OGTTs and we were obliged to use the positive predictive value of the screen to estimate potential cases of GDM in this group.

In conclusion, the James Bay Cree are definitely at an increased risk for GDM compared to the general North American population. They have the second highest prevalence of GDM reported for an aboriginal group worldwide. The high rate of GDM among the James Bay Cree is of concern, as approximately 60% of these women may develop Type 2 diabetes subsequently (3). Therefore universal screening for GDM is important for this population. Whether this high prevalence reflects a greater genetic propensity for diabetes or an elevated level of risk factors for GDM among certain Native populations remains to be determined.

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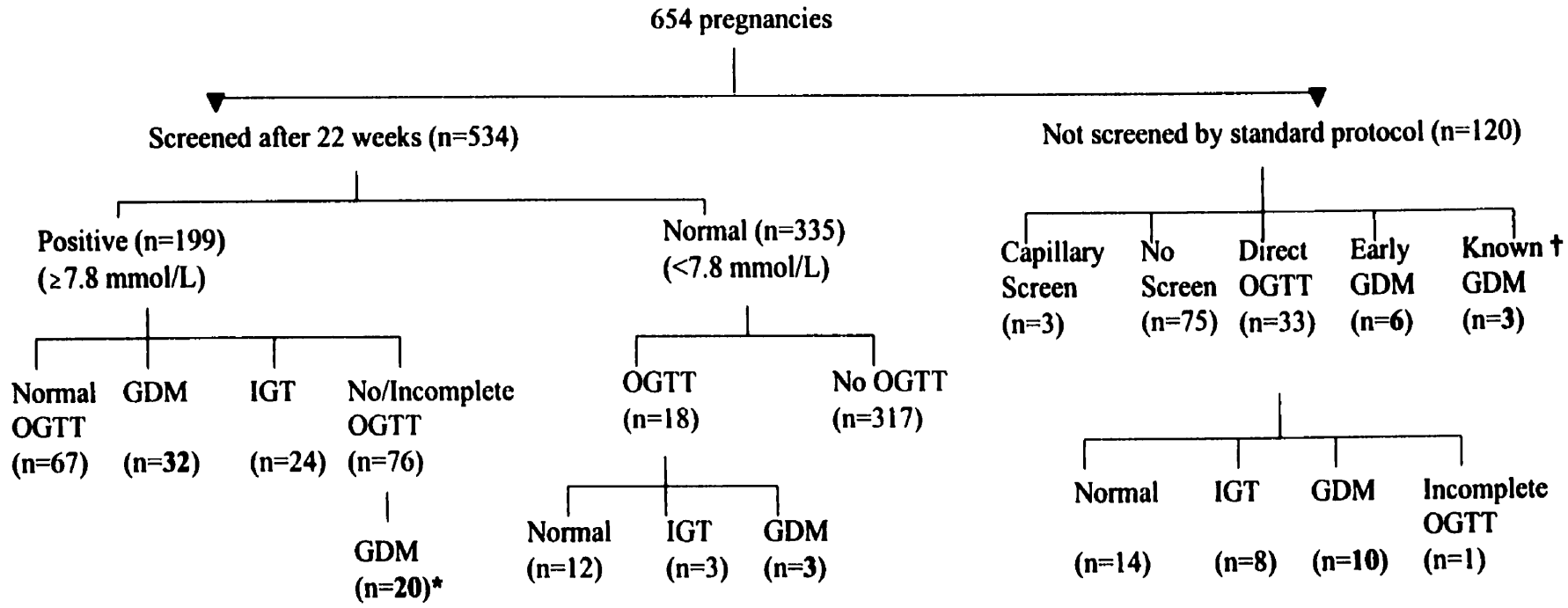
Pima Indians. *Diabetes Care* 1980; 3: 458-64.

Figure 1. Screening and diagnosis of GDM among the Eastern James Bay Cree



* Estimated using the positive predictive value of the screen

† Cases of GDM diagnosed outside the community

The prevalence of 12.8% is based on 32+20+3+3+10+6/579=74/579=12.8% (95% CI: 10.1-15.5)

Table 1: General Characteristics of Cree Women by Screen Status

Maternal Characteristics	Screenees			Total Screened	Not Screened
	Normal	*GDM, IGT*	*+ve screen, no OGTT*		
Age (y)	23.1±5.1[•]	27.4±6.2[†]	25.6±6.1[†]	24.0±5.7	24.1±5.6
	n=413	*n=89*	*n=77*	*n=579*	*n=75*
Parity	1.4±1.4[•]	2.0±1.9[†]	1.8±1.6[•†]	1.6±1.6	1.6±1.6
	n=412	*n=89*	*n=77*	*n=578*	*n=75*
Pregravid wt (kg)	78.9±18.5[•]	84.8±18.6[†]	86.4±13.5[†]	80.9±18.2	79.9±18.9
	n=261	*n=67*	*n=47*	*n=375*	*n=42*
Term birth weight (g)	3800±505[•]	4012±532[†]	3851±476[•†]	3839±510	3835±459
	n=394	n=86	n=67	n=547	n=57

Data are expressed as Mean ± SD

Groups with different superscripts are statistically different at $p<0.05$ using Tukey's Studentized Range (HSD) test or Student's t-test

LINKAGE STATEMENT

Chapter 3 established that the Cree of James Bay have a high prevalence of GDM at 12.8%, the second highest prevalence reported for an Aboriginal group worldwide. It also clearly showed that although Cree women were very young on average (23 y), their pregravid body weight was very high (81 kg) and more than half of them were obese at the start of pregnancy (55.5%). This is not the case in the general North American population, where childbearing is normally delayed and such high rates of obesity are generally not seen among younger women. It is unclear whether the elevated prevalence of GDM among the Cree compared to a prevalence of 3-5% reported for the general North American population is due to the very different risk profiles for GDM between the two populations. The second study (chapter 4) was thus designed to address this question. Specifically, independent risk factors for GDM were identified among the Cree and the risk for GDM was compared between Cree and non-Native women after statistically controlling for differences in the distributions of risk factors or after frequency-matching Cree women with non-Native women for major risk factors.

CHAPTER 4

INTERACTION OF BODY WEIGHT AND ETHNICITY ON RISK OF GESTATIONAL DIABETES MELLITUS

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4.1 Abstract

Background: The James Bay Cree (Canada) have one of the highest recorded rates of gestational diabetes mellitus (GDM) among Aboriginal peoples worldwide; the reasons for this elevated risk remain to be documented.

Objective: To compare predictors and risk of GDM between the James Bay Cree and non-Native Canadians.

Design: Risk for GDM was compared between Cree and non-Native women by a) statistically adjusting for differences in age, parity, pregravid weight, and smoking status (n=402 Cree, 7718 non-Natives); b) matching Cree women with non-Native women for age and pregravid weight (n=394 Cree, 788 non-Natives). Dietary and physical activity information was available for a subset of Cree women (n=152).

Results: Age and pregravid weight were independent predictors of GDM in both Cree and non-Native women. After controlling for these predictors, normal-weight (≤77 kg) Cree women were not at increased risk for GDM (OR: 1.42, 95% CI: 0.67-2.71) but overweight Cree women had an elevated risk compared with overweight non-Native women (OR: 2.25, 95% CI: 1.32-3.80).

Conclusions: Overweight Cree women are at increased risk for GDM. Given the high prevalence of pregravid overweight among the Cree, the burden of GDM is higher than among non-Native Canadians.

4.2 Introduction

Gestational Diabetes Mellitus (GDM) defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" (1), afflicts approximately 3-5 % of women in the general North American population, with higher rates being reported among specific ethnic groups such as Blacks, Hispanics, Asians and Orientals compared to non-Hispanic Whites (2-6). A high prevalence of GDM has also been reported among several North American Native groups (7-9), but the reason(s) for this high prevalence compared to the general population is unknown. GDM increases the risk for pregnancy complications and subsequent Type 2 diabetes in the mother and her offspring (10-11). The high rates of GDM among Native groups are of concern given their young age and the likelihood of early onset of Type 2 diabetes.

Independent predictors of GDM identified in multi-ethnic populations include age (2-5), parity (5), prepregnancy body mass (2-5), prepregnancy and pregnancy waist-to-hip ratio (12-13), prepregnancy smoking status (4), and weight gain during early adulthood (4). The elevated prevalence of GDM reported for some ethnic minority groups such as Hispanics, Blacks and Orientals compared to Caucasians persist even after controlling for some of the aforementioned predictors, namely age and body weight (2-6). The high prevalence of GDM reported for some North American Native groups compared with the general population may be due to a disproportionate distribution of risk factors for GDM in the two populations, genetic predisposition among the former, or both, and needs to be investigated.

The purpose of this study was therefore a) to identify and compare predictors of GDM among the Cree of eastern James Bay, Canada, who have a high prevalence of GDM (9), to the general Canadian population using a large obstetric database of non-Native pregnancies, b) to determine whether differences in GDM prevalence between the Cree and the general Canadian population could be explained by differences in the GDM risk profiles of age, parity, height, pregravid weight/body mass index and smoking status between the two populations.

4.3 Subjects and Methods

About 11,000 Cree live in 9 communities east of James Bay (northern Quebec). Of these, 7 communities are accessible by year-round roads. The size of the communities varies from 485 to 2951 inhabitants (14). Traditionally, the Cree were hunter-gatherers. The establishment of the hydro-electric project in James Bay in 1975 led to the beginning of a more settled existence for the Cree. At present, all houses have electricity and modern appliances but are often overcrowded. Although traditional foods such as wild game and fish are still highly valued, traditional dietary patterns have changed, with the younger generation consuming predominantly market foods (15). The recent lifestyle changes have been accompanied by high rates of obesity and Type 2 diabetes, especially among Cree women (16).

4.3.1 Data collection

Maternal medical charts for all Cree deliveries from January 1995-December 1996, in the 9 communities of James Bay (n=681) were reviewed for obstetrical information. Data for non-Native Canadian pregnancies were extracted from the McGill Obstetric and Neonatal Database (MOND), which is a computerized database of all deliveries at the Royal Victoria Hospital (Montreal, Canada) since 1978. The hospital serves a multi-ethnic Montreal population. Less than 1% of 71,415 First Nations people in Quebec, live in Montreal (17).

Diagnosis of gestational diabetes mellitus (GDM) among the Cree and at the Royal Victoria Hospital, Montreal, was in accordance with the National Diabetes Data Group recommendations (18). Specifically, women were screened with a 50 g oral glucose load between 24-30 weeks gestation. If the plasma glucose value at 1-h was $\geq$7.8 mmol/L, the patient was asked to undergo a 100 g 3-h oral glucose tolerance test (OGTT) after an overnight fast. GDM was diagnosed if any 2 of the 4 values on the OGTT were met or exceeded (fasting: 5.8, 1-h: 10.6, 2-h: 9.2, 3-h: 8.1 mmol/L). Information on the following variables of interest were obtained for both populations: diabetes status, mother's date of birth, pregravid weight, height, parity, and smoking status during pregnancy. Women with pregestational diabetes, uncertain GDM status due to missing screen or OGTT information,

preterm birth, a spontaneous abortion and those on glucocorticoid therapy were excluded from the analyses. In addition, high-risk referrals from other hospitals were also excluded from MOND. Ethical approval for the study was obtained from the Human Ethics Review Board of McGill University.

Of the 681 deliveries among the Cree, 499 met the inclusion criteria. Of these, pregravid weight information was missing for 85 pregnancies, parity information was missing for 1 pregnancy, maternal smoking status was unknown for 11 pregnancies and height information was missing for 138 pregnancies. Therefore, complete information on maternal age, pregravid weight, parity, and smoking status was available for 402 pregnancies, with 16 women contributing two pregnancies between January 1995-December 1996. If height was included as a predictor, complete information was available for 264 pregnancies. Women with missing information on pregravid weight or height were similar in most characteristics to women with complete data. The one exception was that women with no information on height (n=138) had a lower prevalence of GDM compared with women with complete data (n=264) (4.4% vs. 15.2%, $p< 0.001$).

Pregravid weight information for Cree women was based on maternal recall (147/402) (if within 5 kg of measured weight up to 10 weeks gestation or within 7 kg of measured weight between 10-20 weeks gestation) or the first available weight up to 20 weeks gestation (255/402). Height was either measured (174/264) or based on maternal report at booking (90/264). High correlations between self-reported and measured weights and heights have been reported in population based studies (19-20).

Information on parity and smoking status was based on maternal report. Information on diet, physical activity patterns and rate of weight gain before GDM diagnosis and GDM status in the previous pregnancy was available in a subset of Cree women (n=152). In analyses of this subset, women with impaired glucose tolerance (IGT) (one abnormal value on the 3-h 100 g OGTT) were pooled with GDM women to increase statistical power (n=24 GDM/IGT, 128 normoglycemic women). Women in the Cree subset (n=152) were not different in age, parity, pregravid weight, height and smoking status compared with women in the entire Cree sample with complete data (n=402) ($p>0.05$). Energy and macronutrient

intakes were estimated from a single 24-h recall before GDM diagnosis using Food Processor II, Version 5.03 (ESHA Research, Salem, Oregon, USA). Physical activity patterns were determined from a questionnaire administered at the time of the 24-h recall, to categorize women into sedentary or active, based on frequency of participation in various activities (21). In order to determine rate of weight gain before GDM diagnosis in the Cree subset, last available weight before GDM/IGT diagnosis was deducted from the first available pregnancy weight and then divided by the number of weeks elapsed for GDM women. As normoglycemic women did not undergo an OGTT, the last available weight before the median gestational age at which the OGTT was administered in the GDM/IGT group was used as the last weight. Information on previous GDM was based on maternal reports and validated against laboratory reports of glucose screening in the previous pregnancy when available.

Of the 20,982 deliveries in the MOND (1990-1996), 20,619 met the inclusion criteria. In addition, the data were restricted to women born in North America or Europe to limit ethnic heterogeneity of the sample, as no other indicators of ethnicity were available in this database. This reduced the sample size to 13,734 pregnancies. Of these, no information on pregravid weight was available for 5864 pregnancies, information on maternal smoking status was unknown for 152 pregnancies and height information was missing for 1,483 pregnancies. Therefore, complete information on maternal age, parity, pregravid weight and smoking status was available for 7718 non-Native pregnancies, with 800 women contributing two pregnancies, 45 women contributing three pregnancies and 4 women contributing four pregnancies over the time period studied. If height was included as a predictor, the sample size decreased to 6235 pregnancies. The only difference between non-Native women with missing data for pregravid weight or height and women with complete data was that GDM prevalence was lower by 3.7-4.1% ($p<0.001$) among women with missing information on these variables. In the MOND population, information on pregravid weight, height, parity and smoking status were based on maternal reports at hospital booking. No information on previous GDM, rate of weight gain before GDM diagnosis, diet or physical activity patterns was available from this database.

Because of the large number of missing heights for both Cree and non-Native women, obesity was defined as pregravid weight >77 kg, which is equivalent to BMI >29 kg/m^2 (recommended as the obesity cut-off by the Institute of Medicine of the US (22)) for a woman of average stature (1.6 m for both Cree and non-Native women).

4.3.2 Data analyses

The primary outcome was the presence or absence of GDM. The following predictor variables were evaluated for their effects on GDM risk for Cree (n=402) and non-Native (n= 7718) women separately: age, pregravid weight, and smoking status. In order to determine the effects of ethnicity (Cree vs. non-Native) on GDM, data for the two ethnic groups were pooled together and the effect of ethnicity on GDM was determined in multivariate analyses adjusting for the effects of age, pregravid weight and smoking status.

Cree and non-Native women were also frequency matched on a 1 : 2 basis for pregravid weight (± 2.5 kg) and age (± 10 y), to control for differences in the distribution of these two variables. Even with a large non-Native database and a wide margin for age, we could not find appropriate pregravid weight matches for 8 young Cree women who were very overweight, and these were therefore excluded. The final sample size for the matched sample was thus 394 Cree women and 788 non-Native women.

All analyses were repeated a) substituting height and BMI in the model for pregravid weight (n=264 Cree and 6235 non-Natives for the unmatched sample and n=258 Cree and 623 non-Natives for the matched sample); b) restricting the data to only the most recent pregnancy among women with repeat pregnancies over the study period (n=386 Cree and 6816 non-Natives). The magnitude of risk associated with previous GDM, rate of weight gain, energy and macronutrient intakes and physical activity levels before GDM diagnosis were evaluated for the Cree subset (n=152).

Student's independent t-test and the chi-square test were used to test differences between continuous and categorical variables, respectively. Multiple logistic regression analysis was used to estimate adjusted odds ratios and 95% confidence intervals. The Breslow-Day test of homogeneity of odds ratios across strata of ethnicity was used to explore

interactions between ethnicity and other predictors of GDM. The level of significance was set at $p \leq 0.05$ for all predictors and at $p \leq 0.1$ to detect interactions between predictors. All analyses were conducted using the Statistical Analysis System (SAS, version 6.12, NC, USA).

4.4 Results

Clinical and socio-demographic profiles of the Cree and non-Native samples are presented in Table 1. In the unmatched sample, the prevalence of GDM among Cree women (n=402) was 11.4% vs. 5.3% among non-Native women (n=7718). Risk profiles for GDM were very different between the two populations, with the Cree being younger, more parous and heavier. More than half the Cree women were classified as obese (pregravid weight >77 kg) compared with only 10% of non-Native women. Although there were more smokers among the Cree, the average number of cigarettes smoked per day by smokers was lower (5 vs. 13 cigarettes respectively). In the matched sample (n=394 Cree and 788 non-Natives), pregravid weight and BMI was not different between the two ethnic groups, as expected, given the narrow pregravid weight margin used for matching (± 2.5 kg). However, Cree women in the matched sample were significantly younger and more parous than non-Native women whereas GDM prevalence was no longer significantly different between the two groups (11.4% vs. 8.1%). In both the unmatched and matched samples, Cree women delivered heavier infants than non-Native women (Table 1). However, while infant birth weight was significantly higher among Cree women with GDM compared with normoglycemic Cree women (4171 ± 496 g vs. 3797 ± 529 g, $p<0.0001$), this was not the case among non-Native women (3479 ● 480 g vs. 3501 ± 458 g, $p=0.37$).

Table 2 shows independent risk factors for GDM stratified by ethnicity in the matched and unmatched samples. Risk factors that were significantly associated with GDM among the Cree in the unmatched sample (n=402) were age and pregravid weight, whereas parity and smoking status did not attain statistical significance. When BMI and height were substituted for pregravid weight in the same model, BMI was a significant predictor (adjusted OR per 5 kg/m^2: 1.33, 95% CI:1.04-1.71), whereas height was not (adjusted OR

per 5 cm: 1.04, 95% CI: 0.73-1.48). Similar results were obtained for the matched Cree sample (n=394). Among unmatched non-Native women, all risk factors evaluated, i.e. age, parity, body weight and smoking status were significantly associated with GDM (Table 2). When the model was rerun after substituting BMI and height for pregravid weight, both were statistically significant (adjusted OR per 5 kg/m^2 of BMI: 1.50, 95% CI: 1.36-1.65, adjusted OR per 5 cm of height: 0.83, 95% CI: 0.77-0.89). The results were similar for the matched non-Native sample (n=788), except that the effects of parity, height and smoking status were no longer statistically significant.

In multiple logistic regression analysis pooling data for the two ethnic groups (n=402 Cree and 7718 non-Natives), and including ethnicity, age, parity, pregravid weight and smoking status in the model simultaneously, a significant interaction was noted between ethnicity and pregravid weight or BMI (Figure 1). The adjusted odds ratio for the interaction between ethnicity and BMI was 1.45 (95% CI: 1.02-2.07). Interactions between ethnicity and other predictors in the model were not significant.

Further analyses were conducted after stratification by pregravid weight ($\leq$77 kg, >77 kg) because of the observed interaction between weight and ethnicity. The magnitude of risk for GDM imparted by each risk factor after adjusting for the effects of other risk factors stratified by pregravid weight is shown in Table 3, for both the unmatched and matched samples. Ethnic status was not a significant predictor of GDM among normal-weight individuals for either the matched or unmatched samples, which implies that normal weight Cree women had a similar risk for GDM as normal weight non-Native women. In contrast, ethnic status had a significant effect among obese women (matched and unmatched samples). Even after adjusting for age, parity, pregravid weight and smoking status, the risk for GDM more than doubled for obese Cree women compared with obese non-Native women (Table 3). The same effect was seen when the model was rerun after stratification by BMI instead of pregravid weight and also adjusting for height.

When the analyses were repeated after restricting the data to the most recent pregnancy among women with repeat pregnancies during the study period (n=386 Cree and 6816 non-Natives), the results were very similar (data not shown).

Risk factors for GDM were also analyzed for the Cree subset (n=152) with information on diet and physical activity prior to GDM diagnosis. In univariate analyses, Cree women with GDM/IGT (n=24) had a higher frequency of GDM in the previous pregnancy (29.2% vs. 3.2%, $p<0.001$), significantly lower prediagnostic rate of weight gain (Mean ± SD: 0.36 ± 0.20 vs. 0.50 ± 0.29 kg/week, $p<0.01$) and lower energy consumption (Mean ± SD: 9301 ± 3402 vs. 11,958 ± 3619 kJ, $p=0.001$), whereas physical activity patterns were not different (54% vs. 42% sedentary, $p=0.26$) compared with normoglycemic women (n=128). In multivariate analyses in the Cree subset (n=152), independent predictors of GDM were age (adjusted OR per 5 y: 1.85, 95% CI: 1.22-2.87), BMI (>29 vs. ≤29 kg/m^2, adjusted OR: 3.52, 95% CI: 1.19-12.06) and energy intake (adjusted OR per 100 kcal or 418 kJ: 0.92, 95% CI: 0.86-0.98). When previous GDM (adjusted OR: 7.42, 1.60-41.75) was added to the model, the odds ratios for energy intake, age and BMI remained unaffected. After adjusting for age, BMI, energy intake and previous GDM, none of the other variables (i.e. parity, smoking status, rate of weight gain and individual macronutrients) were statistically significant ($p>0.1$).

4.5 Discussion

The aim of this study was to compare risk for GDM between Cree women and non-Native women in the general Canadian population after accounting for differences in age, parity, body mass and smoking status. Our results indicated that only obese Cree women were at a higher risk for GDM compared with obese non-Native women, whereas GDM prevalence was similar among normal weight Cree and non-Native women. Ethnic differences in GDM risk have been shown in other studies, where a high prevalence of GDM was noted among ethnic minority groups such as Blacks, Chinese, Hispanics and Asian-Indians compared to Caucasians in the United kingdom or United States, even after controlling for differences in age, parity and body weight (2-6). However, our study is the first to report an interaction between body weight and ethnicity as a determinant of GDM and to document differences between Aboriginal and non-Native women.

Independent predictors of GDM among the Cree were similar to those among non-

Native women in the general Canadian population. Among the Cree, older and heavier women were at increased risk for GDM. This is supported by a study on the Cree and Ojibwa Natives of the Sioux Lookout Zone in northwestern Ontario, Canada (the only other study on predictors of GDM in a North American Native group) (8) and by other reports among multi-ethnic populations (2-6). However, unlike observations among the Natives of Sioux Lookout Zone, in our study, parity was not an independent predictor of GDM among the Cree. It is difficult to dissociate the effect of parity from age and BMI effects, as is evident from the existing literature, where most studies do not report parity as an independent risk factor for GDM after adjusting for age and BMI (2-4).

The increased risk for GDM among obese Cree women compared with obese women in the general population could not be explained by differences in age, parity, height, body weight or smoking status. Potential explanations could be differences in diet, physical activity patterns, body fat patterning or genetic predisposition to diabetes. Although information on diet and physical activity patterns during pregnancy was available on a subset of Cree women, no such information was available for our non-Native women. Lower energy intake predicted an increased risk for GDM in the Cree subset (n=1 52) independently of age, previous GDM and body mass. The inverse association between energy intake and GDM risk may be due to underreporting of total energy intake by obese Cree women. Alternatively, obese women may have decreased their energy intake to restrict weight gain during pregnancy. However, even though energy intakes were estimated from a single 24-h recall, we believe that the energy intakes observed among Cree women are a reasonably accurate reflection of their usual intakes during pregnancy for the following reasons: a) a significant positive association was noted between energy intake and weight gain ($r=0.26$, $p=0.002$, $n=144$) in our Cree subset; b) because the 24-h recall was done before GDM diagnosis, there is no possibility of contamination by treatment; c) a single 24-h recall has been reported to accurately reflect group intake in young women (23).

The lower energy intakes seen in our study may be a marker for lower physical activity levels. This inference is reasonable for a number of reasons: First, an inverse association has also been reported between energy intake or physical activity and chronic

diseases such as Type 2 diabetes (24-25) and coronary heart disease (26). Second, aboriginal people who lead traditional lifestyles which include hard physical labor have very low rates of diabetes compared to their genetically linked kin who are more modernized and sedentary (27-28). In addition, even small increases in presumed energy expenditure through hunting and trapping in bush camps were reported to decrease plasma glucose and glycosylated hemoglobin levels among diabetic Cree men and women (29). Third, although physical activity level as measured by a questionnaire was not an independent predictor of GDM in our study, an inverse association was observed between physical activity and obesity in our Cree subset, with obese women reporting more sedentary behaviors ($p<0.001$). Thus, lower physical activity levels among obese Cree women in our study may be one of the reasons for the higher GDM prevalence compared with obese women in the general population, who may be more active. Careful determination of physical activity patterns of obese women in the general population should help shed light on this issue. Further, more precise measures of physical activity during pregnancy need to be developed to explore the relationship between physical activity and GDM.

Another reason for differences in GDM prevalence between obese Cree and obese non-Native women may be due to differences in body fat patterning, which may be genetically predetermined (30-31). Central adiposity as determined by waist-hip ratio or waist circumference has been reported to be an independent predictor of GDM in recent studies (12-13). No information on body fat patterning was available for our study women, but this is a possibility that requires further investigation.

Certain limitations of our study need to be acknowledged. Ethnic characteristics of our non-Native women could not be distinctly documented. However, limiting data to women born in North America and Europe restricted the ethnic heterogeneity of the non-Native sample. Although the possibility of some Cree women being included in the non-Native database cannot be completely ruled out, those evacuated to Montreal because of a high-risk pregnancy were excluded because they were classified as high-risk referrals. Another limitation may be the use of pregravid weight/BMI as an adiposity index in this study. However, good correlations between BMI and percent body fat determined by

densitometry have been reported among non-pregnant (r=0.60-0.82) (32) and pregnant women (correlation between pregravid BMI & percent fat: 0.69) (33). Moreover, our use of a relatively high cut-off to define obesity (BMI >29 or pregravid weight >77 kg) decreases the likelihood of misclassification (34). There were also a large number of missing data on pregravid weight or height for Cree and non-Native women. However, most characteristics were similar between women with missing information and women with complete data, except for a lower prevalence of GDM in the former group. This is likely due to better follow-up and more complete medical records for women with GDM.

In conclusion, our study clearly demonstrates that the high rate of GDM seen among the Cree compared to the general Canadian population is due to a high prevalence of obesity compounded by a higher rate of GDM among obese Cree women. In contrast, Cree women who are not obese are not at a higher risk for GDM than non-Native Canadians. The reasons why obese Cree women are at a much higher risk for GDM than obese women in the general population need to be studied. Also, comprehensive efforts to tackle pregravid obesity among the Cree need to be undertaken through culturally acceptable ways of modifying diet and increasing physical activity (35).

4.6 Acknowledgments

The authors would like to thank the Cree Board of Health and Social Services of James Bay and the Cree Nation Councils for permission to conduct the study and Dr. Robert H. Usher, Royal Victoria Hospital, Montreal, for granting access to the McGill Obstetric and Neonatal Database. We are also grateful to all health personnel in the 9 communities of James Bay for assistance with the project. In particular, we would like to thank Kinga David, Aileen Collier, Helen Smeja, Lucie Leclerc, Emily Bobbish-Rondeau, Pauline Langdon, Nellie Bobbish, Pauline Bobbish, Irene Mistacheesick, Lillian Stewart, Nathalie Gallant, Annie Bosum, Jane Loon, Helen Iserhoff, Beatrice Petawabano, Luce Bourassa, Mary Rabbitskin, Christine Longchap, Rita Mianscum, Paul Linton, Emily Gull and Harriet Charles. We would also like to express our gratitude to all study participants who made this project possible.

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Figure 1. Interaction between Pregravid Weight and Ethnicity

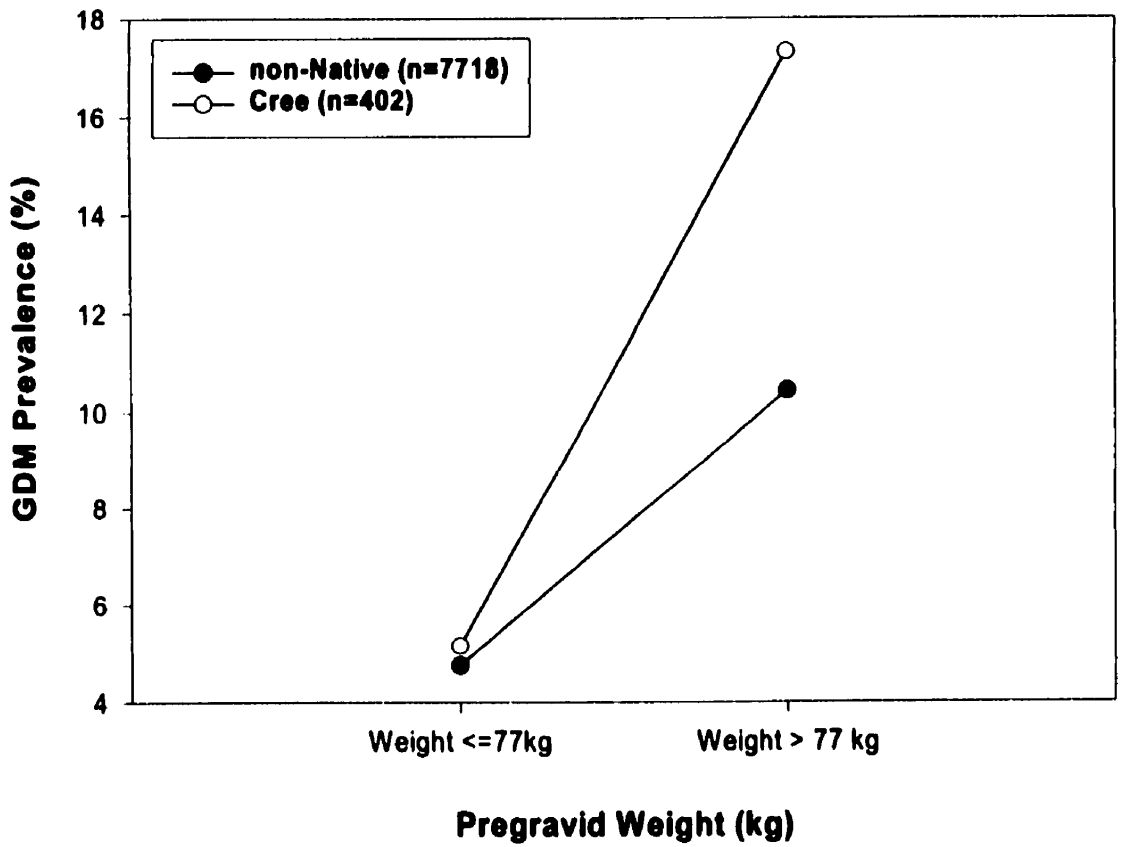

Table 1. General Characteristics of Study Population by Ethnicity[1]

Characteristic	Unmatched Sample			Matched Sample		
	Cree (n=402)	non-Native (n=7718)	*P*	Cree (n=394)	non-Native (n=788)	*P*
Age (y)	23.9 ± 5.7	30.3 ± 4.7	0.0001	23.9 ± 5.7	26.6 ± 4.8	0.0001
Parity, (% primiparous)	57.5	84.3	0.001	57.4	88.6	0.001
Height (cm)	162.4 ± 5.5	163.8 ± 6.7	0.0001[2]	162.1 ± 6.53	165.4 ± 6.8	0.0001[3]
Pregravid weight (kg)	79.6 ± 18.1	62.0 ± 11.8	0.0001	78.3 ± 16.0	78.3 ± 16.0	NS
Pregravid Weight: ≤77 kg (%)	48.3	90.0	0.001[4]	49.2	49.2	NS[4]
>77 kg (%)	51.7	10.0		50.8	50.8	
Body Mass Index (kg/m^2)	30.3 ± 6.8	23.1 ± 4.3	0.0001[2]	29.8 ± 6.0	28.7 ± 6.0	0.02[3]
BMI: ≤26, (%)	28.4	81.5		29.8	35.5	
>26-29, (%)	17.6	8.9	0.001[4]	17.8	18.6	NS[4]
> 29 (%)	54.0	9.6		52.3	45.9	
GDM Prevalence (%)	11.4	5.3	0.001	11.4	8.1	NS
Smokers (%)	45.5	19.2	0.001	45.7	24.4	0.001

[1] Mean ± SD, [2] n=264 Cree & 6235 non-Natives, [3] n=258 Cree & 623 non-natives, [4] Chi-square test

Table 2. Independent Risk Factors for GDM Stratified by Ethnicity [1]

Characteristics	Unmatched Sample		Matched Sample	
	Cree (n=402)	non-Native (n=7718)	Cree (n=394)	non-Native (n=788)
Age (per 5 y)	1.70 (1.25-2.33)	1.46 (1.31-1.63)	1.66 (1.22-2.30)	1.43 (1.07-1.93)
Parity (primi. vs. multiparous)	0.85 (0.40-1.82)	1.40 (1.09-1.78)	0.86 (0.39-1.86)	1.24 (0.59-2.44)
Pregravid weight (per 5 kg)	1.11 (1.03-1.21)	1.13 (1.09-1.17)	1.18 (1.06-1.30)	1.09 (1.01-1.19)
Smoking status (yes/no)	0.81 (0.41-1.58)	1.43 (1.12-1.80)	0.77 (0.38-1.51)	0.96 (0.51-1.73)

[1] Adjusted Odds Ratio (95% Confidence Interval) using Multiple Logistic Regression Analysis

Table 3. Independent Risk Factors for GDM Stratified by Pregravid Weight [1]

Characteristic	Unmatched Sample		Matched Sample	
	Weight ≤ 77 kg (n=7137)	Weight > 77 kg (n=983)	Weight ≤77 kg (n=582)	Weight >77 kg (n=600)
Ethnic status (Cree vs. non-Native)	1.42 (0.67-2.71)	2.25 (1.32-3.80)	1.05 (0.40-2.61)	2.41 (1.34-4.39)
Age (per 5 y)	1.46 (1.30-1.65)	1.52 (1.24-1.87)	1.48 (1.01-2.13)	1.55 (1.19-2.02)
Parity (primi vs.multiparous)	1.38 (1.05-1.79)	1.24 (0.79-1.94)	0.95 (0.28-2.90)	1.09 (0.60-1.93)
Pregravid weight (per 5 kg)	1.10 (1.02-1.18)	1.09 (1.02-1.18)	1.18 (0.91-1.55)	1.10 (1.00-1.22)
Smokers (yes/no)	1.41 (1.08-1.83)	1.15 (0.73-1.77)	1.07 (0.47-2.33)	0.78 (0.43-1.35)

[1] Adjusted Odds Ratio (95% Confidence Interval) using Multiple Logistic Regression Analysis

LINKAGE STATEMENT

The perinatal health status of Native peoples in North America is compromised compared with the general North American population. Infant and post-neonatal mortality rates are elevated among North American Native peoples despite a low prevalence of low birth weight. In contrast, infant macrosomia rates are very elevated and the reason(s) for this have not been investigated adequately.

The average birth weight of Cree infants is the highest reported for any ethnic group in the world. Factors contributing to the large size of the Cree infants at birth have not been determined. From chapters 3 and 4 it is evident that the Cree have a high prevalence of pregravid obesity (55.5%) and GDM (12.8%), despite their young age, and that obese Cree women are at increased risk for GDM compared with non-Native women of similar body weight. Both pregravid obesity and GDM are important risk factors for infant macrosomia, and it is unclear whether the increased prevalence of these indicators alone among the Cree can explain their elevated prevalence of infant macrosomia compared with non-Native Canadian women. Chapter 5 explores independent determinants of macrosomia among the Cree, the relative magnitude of impact of these determinants among Cree vs. non-Native women and the risk for macrosomia among Cree vs. non-Native women after carefully adjusting for differences in risk factors for this outcome.

CHAPTER 5

ETHNIC DIFFERENCES IN PREVALENCE AND PREDICTORS OF INFANT MACROSOMIA

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Journal

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5.1 Abstract

Background: The Cree of James Bay have the highest ever reported mean birth weight and a high prevalence of infant macrosomia.

Objectives: To examine independent risk factors for infant macrosomia among the Cree of James Bay, compare these to risk factors among non-Native Canadians, and determine if ethnic differences persist after adjusting for differences in the distribution of other risk factors.

Study Design: Macrosomia was defined as birth weight >90th percentile for gestational age and sex. Independent determinants of macrosomia were examined in 385 Cree women and 5644 non-Native women. The effect of ethnicity (Cree vs. non-Native) was determined after statistically adjusting for age, parity, pregravid weight, height, gestational weight gain, gestational diabetes (GDM) and smoking status.

Results: The prevalence of macrosomia among the Cree was 34.3% vs. 11.1% among non-Natives. Pregravid weight, height and GDM were independent determinants of macrosomia among the Cree, whereas age, parity, pregravid weight, height and non-smoking status had independent effects among non-Natives. GDM significantly increased the risk for macrosomia among the Cree (odds ratio: 4.46, 95% CI: 2.24-9.26) but not among non-Natives (odds ratio:1.15, 95% CI: 0.79-1.65). The risk for infant macrosomia remained elevated among the Cree compared with non-Natives after adjusting for other risk factors (odds ratio: 3.64, 95% CI: 2.69-4.90).

Conclusions: The high rates of infant macrosomia among the Cree, despite controlling for important differences in pregravid weight and GDM, may reflect genetic differences in fetal growth. GDM was an important risk factor of macrosomia among the Cree but not non-Native Canadians.

5.2 Introduction

Infant macrosomia carries an increased risk for operative delivery, birth trauma and injury, and infant morbidity, especially if associated with maternal diabetes (1-3). The long-term consequences of infant macrosomia are not clear, with some authors reporting subsequent obesity (4-7) but others refuting this finding (8).

Infant macrosomia has been variably defined as birth weight >4000 g, >4500 g or >90th percentile for gestational age and sex (9-10). High macrosomia rates (birth weight >4000 g) of 16 -31% have been reported among several North American Native groups (11-16) compared with approximately 10% in the general North American population (2). Predictors of infant macrosomia in the general population include advanced maternal age, multiparity, pregravid overweight, tall stature, excessive gestational weight gain, diabetes, male sex of the infant, and post-maturity (17). It is unclear whether the high prevalence of macrosomia seen among North American Native groups is attributable to differences in the distribution of risk factors for infant macrosomia, including maternal weight and gestational diabetes mellitus (GDM). Recently, elevated rates of GDM have been reported among several Native groups in North America (18-20). Alternatively, the high mean birth weight of Native infants may be genetic.

The Cree of Eastern James Bay have a high prevalence of GDM at 12.8% (19), and approximately 36% of their infants weighed ≥4000 g at birth (11). The present study was thus designed to examine predictors of infant macrosomia among Cree women, compare these to predictors in the general Canadian population and determine whether differences in macrosomia prevalence between the two populations could be explained by differences in maternal age, pregravid weight, height, gestational weight gain, gestational length, glycemic status, and smoking status.

5.3 Materials and Methods

5.3.1 Study populations

The Cree of James Bay belong to the Algonquian language family and subarctic culture area (21). About 11,000 Cree now occupy 9 communities in James Bay (northern

Quebec). Most communities are accessible by year-round roads. All women have good access to prenatal care which is provided by physicians and nurses at the local community clinics in each village. Most deliveries are done at the northern Quebec hospitals, namely Val-d'Or, Chibougamou and Chisasibi, all of which have facilities for cesarean sections.

Information on all infants born to Cree women in the 9 communities of eastern James Bay between January 1995 and December 1996 was compiled from two sources: the Government of Quebec's official declaration of births and the birth registry maintained by the Cree Board of Health and Social Services of James Bay. There were 615 births to Cree women in 1995-1996, and data for an additional 66 pregnancies in 1997 were available for participants in a nutrition intervention study ending in June 1997. Information on 681 births was thus available. Data for non-Native Canadian pregnancies from January 1, 1990 to March 31, 1996 (n=20,982) were extracted from the McGill Obstetrics and Neonatal Database (MOND), which is a computerized database of all deliveries at the Royal Victoria Hospital (Montreal, Canada) since 1978 (2). Ethical approval for the study was obtained from the Human Ethics Review Board of McGill University and informed consent was obtained from participants in the nutrition intervention study.

5.3.2 Definitions of variables

The main outcome of interest was infant macrosomia, defined as birth weight >90th percentile for gestational age and sex based on the California reference of William et al. (22). Definitions of macrosomia used in separate analyses were absolute birth weight >4000 g or >4500 g. Predictors of fetal growth were also explored to determine which factors influence birth weight. Information on the following variables of interest was abstracted for both populations: maternal age, parity, pregravid weight, height, weight gain during pregnancy, gestational age at delivery, smoking status and glycemic status during pregnancy. Gestational diabetes mellitus (GDM) among the Cree and non-Natives was defined in accordance with the National Diabetes Data Group (NDDG) criteria (23). As an association between birth weight and maternal glycemic status has been reported at lower levels of glucose intolerance (24), the relationship between birth weight/macrosomia and impaired glucose tolerance

(IGT) was also explored. IGT was defined as one abnormal value on the 100 g 3-h oral glucose tolerance test (24). Gestational age at delivery was based on reported last normal menstrual period if it agreed within 1 week of ultrasound dating done between 16-20 weeks (25); in cases of disagreement >1 week, the latter estimate was used. Weekly rate of net weight gain during pregnancy was calculated as [last recorded weight before delivery (kg)-pregravid weight (kg)-infant birth weight (kg)] / gestational duration (wk). Body mass index (BMI) was calculated as pregravid weight (kg)/height (m^2). Obesity in this study was defined as pregravid weight >77 kg because of the large number of missing heights. This cut-off corresponds with a BMI of 29 kg/m^2 for a woman of average stature (1.6 m for both Cree and non-Native women), recommended as the obesity cut-off by the Institute of Medicine (26). A woman was classified as a smoker if she reported any smoking during pregnancy.

Pregravid weight information for Cree women was based on maternal recall (35.6%) (if within 5 kg of measured weight up to 10 weeks gestation or within 7 kg of measured weight between 10-20 weeks gestation) or the first available weight up to 20 weeks gestation (64.4%). Height was either measured (64.3%) or based on maternal report at booking (35.7%). Information on parity and smoking status was based on maternal report. Information on diet and physical activity patterns during pregnancy was available for a subset of Cree women (n=152) who participated in a nutrition intervention study (July 1995-June 1997). Energy and other macronutrient intakes were estimated from a single 24-h recall at a mean gestational age of 27 ± 4 weeks. Nutrient analysis was based on Food Processor II, Version 5.03 (ESHA Research, Salem, Oregon, USA). Physical activity patterns were determined from a questionnaire administered at the time of the 24-h recall and were used to categorize women into sedentary or active, based on frequency of participation in various activities (27). In the non-Native sample (MOND), information on pregravid weight, height, parity and smoking status was based on maternal reports at hospital booking. No information on diet or physical activity patterns was available from this database.

5.3.3 Inclusion criteria

Only singleton live births were used in the analyses. In addition, the following

exclusion criteria were applied to both populations: preterm births (<37 weeks), pregestational diabetes and glucocorticoid therapy. Further, high-risk referrals from other hospitals and women born outside North America and Europe were excluded from MOND to ensure a sample with a large Caucasian majority. Extreme outliers for weight gain during pregnancy were identified and eliminated using a method described by Tukey (28). As there were only 2 women with a low BMI (<19.8 kg/m^2) among the Cree, women with a BMI <19.8 kg/m^2 were excluded from both samples to make them more comparable.

5.3.4 Sample size

Of the 681 births among the Cree, 475 met the inclusion criteria. Missing data for the following variables decreased the sample size further: parity (n=1), pregravid weight (n=79), smoking status (n=10), and height (n=133). This resulted in a final sample of 385 Cree pregnancies with complete information except height or 252 pregnancies with all information including height. Women in the Cree subset with information on diet and physical activity patterns (n=152) were similar in age, parity, pregravid weight, height, pregnancy weight gain, and smoking status to women in the entire Cree sample with complete data (n=385).

Of the 20,982 births in the MOND, 12,353 met the inclusion criteria. Of these information was missing on pregravid weight for 5833, weight gain on 769, smoking status on 107, and height on 1306. This resulted in a final sample of 5644 MOND pregnancies without missing data for all variables except height and 4338 pregnancies with information on all variables including height.

5.3.5 Statistical analyses

Predictors of both birth weight and macrosomia were assessed in this study. Because height is often not recorded in prenatal files, we initially ran the analyses without height and BMI. All analyses were also rerun substituting height and BMI for pregravid weight (n=4338 non-Natives, n=252 Cree). Analyses were also repeated after restricting the data to the most recent pregnancy for each woman with more than one pregnancy during the study period. Of the 5644 pregnancies to non-Native women, 502 women had 2 pregnancies, 22 women had

3 pregnancies and 2 women had 4 pregnancies between January 1990 to March 1996. Of the 385 pregnancies among the Cree, 15 women had 2 pregnancies between January 1995-December 1996. The sample size in the analysis excluding repeat pregnancies was thus 5092 non-Native and 370 Cree pregnancies.

Student's independent t-test and chi-square tests were used to test group differences between continuous and categorical variables, respectively. Multiple logistic regression analysis was used to examine predictors of infant macrosomia and estimate adjusted odds ratios and 95% confidence intervals. The Breslow-Day test of homogeneity of odds ratios across ethnicity strata was used to explore interactions between ethnicity and other predictors of macrosomia. Multiple linear regression analysis was used to identify predictors of birth weight. The level of significance was set at $p \leq 0.05$ to test for significance of predictors and detect interactions between predictors. All analyses were conducted using the Statistical Analysis System (SAS, version 6.12, NC, USA).

5.4 Results

Maternal characteristics were very different between the two ethnic groups: the Cree were younger (23.9 ± 5.6 vs. 30.5 ± 4.6 y, $p<0.0001$), more likely to be multiparous (42.6% vs. 16.1%, $p<0.001$), obese (52.2% vs. 11.2%, $p<0.001$), and smokers (45.2% vs. 18.0%, $p<0.001$), had higher rates of gestational diabetes (GDM) (11.7% vs. 4.8%, $p<0.001$), but gained less weight during pregnancy (12.3 ± 6.4 vs. 14.9 ± 5.1 kg, $p<0.0001$), and smoked fewer cigarettes per day on average (5 ± 4 vs. 13 ± 8 cigarettes for smokers, $p<0.001$), compared with non-Native women. Birth weight distributions of Cree and non-Native infants are presented in Figure 1. The distribution was shifted to the right for Cree infants; they were heavier than non-Native infants by 338 g on average (3859 ± 519 g vs. 3521 ± 450 g, $p<0.0001$). The groups had comparable gender distribution and length of gestation (39.7 ± 1.2 vs. 39.7 ± 1.2 weeks, $p= 0.78$).

Macrosomia prevalence defined alternatively as birth weight >90th percentile for gestational age or absolute birth weight >4000 g or >4500 g was 34.3%, 37.4% and 11.4% respectively, among the Cree vs. 11.1%, 13.6% and 1.8%, respectively, in the non-Native

sample. Table 1 indicates the prevalence of infant macrosomia by maternal and infant characteristics, stratified by ethnicity. In univariate analysis, infant macrosomia among the Cree was more common among women who were taller, heavier, had GDM, had a longer gestation and did not smoke during pregnancy. Among non-Natives, infant macrosomia was more common among women who were older, multiparous, heavier, taller, had high weight gains and longer gestation, and were non-smokers. However, in almost all strata of predictors, macrosomia was at least twice as high among Cree infants as among non-Native infants. The cesarean section rate among the Cree was not higher among macrosomic vs. non-macrosomic infants, whereas among the non-Natives, cesarean section rates were significantly associated with infant macrosomia (Table 1). The overall cesarean section rate for the Cree was significantly lower than non-Natives (15.7% vs. 20.8%, p=0.02).

Independent predictors of macrosomia for Cree and non-Native women, in multivariate analyses, are presented in Table 2. Significant predictors of macrosomia among the Cree were pregravid weight, and GDM, whereas among non-Natives, age, multiparity, pregravid weight, and net rate of weight gain were positive predictors and smoking during pregnancy was a negative predictor. The odds ratios for most predictors were similar between the Cree and non-Natives given differences in statistical power, with the exception of GDM.

Th risk for macrosomia associated with GDM was very elevated among Cree women and not elevated among non-Native women. This interaction between ethnicity and GDM is illustrated in Figure 2. Cree women with GDM were 4.5 times more likely to have macrosomic babies compared to their normoglycemic counterparts, whereas non-Native women with GDM in this sample had the same risk for infant macrosomia as normoglycemic non-Native women. GDM was associated with an increased mean birth weight among the Cree (4185 ± 492 g vs. 3501 ± 476 g, p<0.0001) while this was not observed in non-Natives (3522 ± 448 g vs. 3501 ± 476 g, p=0.48). Impaired glucose tolerance was not associated with an increased risk for macrosomia either among the Cree or non-Natives. Therefore, women with IGT were pooled with normoglycemic women in the analyses.

Multiparity did not increase the risk for macrosomia among Cree infants but had a

significant effect among non-Native infants. Similarly, net rate of weight gain during pregnancy did not increase the risk for macrosomia among the Cree but was an important predictor among the non-Natives (Table 2). When pregravid BMI and height were substituted for pregravid weight, a 5-unit increase in BMI increased the odds for macrosomia by a factor of 1.29 (95% CI: 1.03-1.65), while a 5-cm increase in height increased the odds for macrosomia by a factor of 1.48 (95% CI: 1.13-1.96) among the Cree. Among non-Natives, for an equivalent increase in BMI and height, the odds ratios for macrosomia were 1.66 (95% CI: 1.48-1.86) and 1.35 (95% CI: 1.26-1.46), respectively. In all analyses performed, the results were very similar when macrosomia was defined as birth weight >4000 g or >4500 g. When analyses were restricted to the most recent pregnancy among Cree (n=370) and non-Native women (n=5092), the results were similar (data not presented). In order to determine the risk for infant macrosomia imparted by ethnicity (Cree vs. non-Native), multiple logistic regression analysis was performed, combining data for the two ethnic groups and adjusting simultaneously for the effects of maternal age, parity, pregravid weight, net weight gain, GDM status, gestational age, and smoking status. The results are presented in Table 3. After controlling for the effects of the other risk factors, Cree infants were 3.6 times more likely to be macrosomic compared to non-Native infants. Multiple linear regression analysis using birth weight as the dependent variable confirmed this finding. In adjusted analyses, Cree infants were heavier than non-Native infants by 235 g on average (3763 ± 25 g vs. 3528 ± 5 g respectively, $p<0.0001$). Similar results were obtained when BMI and height were substituted for pregravid weight in the analyses.

The effect of maternal diet and physical activity during pregnancy on infant birth weight was evaluated for the Cree subset (n=152). Cree women consumed an average of 11,460 ± 3623 kJ/day. The relative contributions of carbohydrate, fat and protein to the total energy intake were 52%, 32% and 16% respectively. Sedentary activity was reported by 43.2% of Cree women. In univariate analyses in the Cree subset (n=152), BMI, height, gestational age at delivery, and GDM status were significant positive predictors of infant birth weight. Total energy intake, percent calories from individual macronutrients and physical activity were not statistically significant in univariate or multivariate analyses.

5.5 Discussion

The aim of this study was to understand why the prevalence of macrosomia is so elevated among the Cree women compared to Canadian non-Native women. The high prevalence of infant macrosomia among the Cree was not fully explained by differences in the distribution of factors that influence fetal growth, i.e. maternal age, pregravid weight, height, gestational weight gain, gestational length, glycemic status, and smoking status. After accounting for ethnic differences in indicators for fetal growth, Cree infants weighed 235 g more than non-Native infants and were at least 3 times more likely to be macrosomic. Our results indicated a large difference in the importance of GDM as a risk factor for macrosomia between Cree and non-Native women. While the risk for macrosomia more than quadrupled for Cree infants whose mothers had gestational diabetes (GDM), non-Native infants were not at increased risk for macrosomia regardless of maternal glycemic status. The prevalence of infant macrosomia among the Cree of 37.4% (birth weight >4000 g) is higher than that reported for different North American Native groups (16-31%) (12-16) or any other ethnic group worldwide .

Pregravid weight, height and GDM were independent predictors of macrosomia among the Cree. This is congruent with other reports in the Native literature (12-16). Several studies among North American Native groups report an increased mean birth weight or macrosomia prevalence among women with GDM. Among the Pima Indians of Arizona (16), the prevalence of infant macrosomia (birth weight >90th percentile for gestational age) was much higher among women with GDM compared with women with normal glucose tolerance (44.4% vs. 17.4%). Similarly, among the Yup'ik Eskimos of Alaska, infants born to women with GDM weighed 149 g more, on average, than infants of negative screenees (14). In a study among the Natives of Sioux-Lookout Zone, Ontario, Canada, the risk for infant macrosomia (birth weight >4000 g) was higher among women with GDM only if they had fasting hyperglycemia (12).

Ethnic differences in the magnitude of effect of maternal diabetes on infant birth weight have been reported between African-Americans and Whites in the United States (29-30). In a recent study (29), maternal diabetes increased mean birth weight by 212 g among

African-American infants vs. 116 g among White infants after adjusting for the effects of maternal place of birth, age, education, parity, prenatal care, hypertension and gestational age. The odds ratio for infant macrosomia (birth weight >4000 g) was 2.98 (2.89-3.12) for African-American infants vs. 1.83 (1.78-1.89) for White infants. However, this finding may be due to ethnic differences in pregravid weight, which were not controlled in this study. This is plausible because the prevalence of obesity among African-American women is higher compared with US-Caucasian women (31), and obesity is a strong determinant of both diabetes (32) and infant macrosomia (33). The type of diabetes or treatment was not specified in the latter study.

Our study is the first to report a significant interaction between ethnicity and GDM as a determinant of macrosomia in well-controlled analyses. We do not know the reason(s) for this ethnic difference in the impact of GDM on risk for macrosomia. One potential explanation may be difference in treatment strategies for GDM between the two ethnic groups. The literature on the effectiveness of GDM treatment in decreasing the incidence of macrosomia is equivocal and very few randomized trials have addressed this issue (34-39). However, there is some evidence from observational studies that intensive management of GDM can decrease the risk for infant macrosomia (40-41). An earlier study at the hospital (RVH) from which our non-Native controls were derived, demonstrated that an intensive treatment regimen for GDM (including weekly monitoring of blood glucose levels by a multi-disciplinary team, home blood glucose monitoring, dietary and weight gain restrictions, and judicious use of insulin) was effective in normalizing birth weight through a reduction in gestational weight gain, and fasting and post-prandial glycemic levels (42). The average birth weight of infants born to women with GDM in the latter study was 3542 g similar to that seen among our non-Native women with GDM (3522 g). Another explanation may be differences in the severity of hyperglycemia between Cree and non-Native women with GDM. However, there is no perception of this by health practitioners in the Cree communities and in fact less Cree women with GDM were treated with insulin compared with non-Native women.

Unlike non-Native women, multiparity, gestational weight gain and cigarette

smoking did not affect infant birth weight among the Cree. The smaller sample size for the Cree may partly account for these differences. The lack of importance of gestational weight gain as an independent predictor of birth weight among the Cree may be related to the high average body weight among Cree women. Overweight women generally gain less weight during pregnancy and gestational weight gain among these women does not have an impact on birth weight to the same extent as among normal weight women (43). Smoking during pregnancy is reported to decrease birth weight by 150-200 g, the impact depending on the number of cigarettes smoked (44-45). Although a higher percentage of Cree women smoked cigarettes during pregnancy compared with non-Native women, the average number of cigarettes smoked per day was lower (5 vs. 13 cigarettes) and may explain why maternal smoking status did not influence birth weight among the Cree.

The high mean birth weight of Cree infants compared to non-Native infants after controlling for differences in maternal and fetal indicators may reflect genetic differences in fetal growth. Despite their low socio-economic status, the Cree have a low birth weight (<2500 g) rate of only 2.6% (11) compared with 5.9% for the general Canadian population (46). The large size of Cree infants may reflect selective survival of large healthy infants through a process of natural selection.

A limitation of this study was the large reduction in sample size for Cree and non-Native women due to missing information on pregravid weight. However, most indicators were similar between non-Native women with missing information for pregravid weight (n=5833) and non-Native women with complete data (n=5644) with the exception that GDM prevalence was lower by 3.3% ($p<0.001$) in the former group. This difference is likely due to better follow-up and more complete medical records for women with GDM. All characteristics of Cree women with missing pregravid weight (n=79) were very similar to Cree women with complete data (n=385), with the exception of a minor difference in mean birth weight (3743 ± 454 vs. 3859 ± 519 g, $p=0.05$).

In conclusion, Cree infants are at a higher risk for infant macrosomia than non-Native infants even after adjusting for the effects of potential confounders. The risk is exacerbated by the high prevalence of GDM and its impact on macrosomia among Cree women. The high

average birth weight and risk for macrosomia among Cree women with GDM calls for a careful evaluation of treatment strategies currently being used among the Cree and their effect on glycemic control. It remains to be determined whether the high prevalence of infant macrosomia among the Cree has any deleterious consequences in the short or long term.

5.6 Acknowledgment

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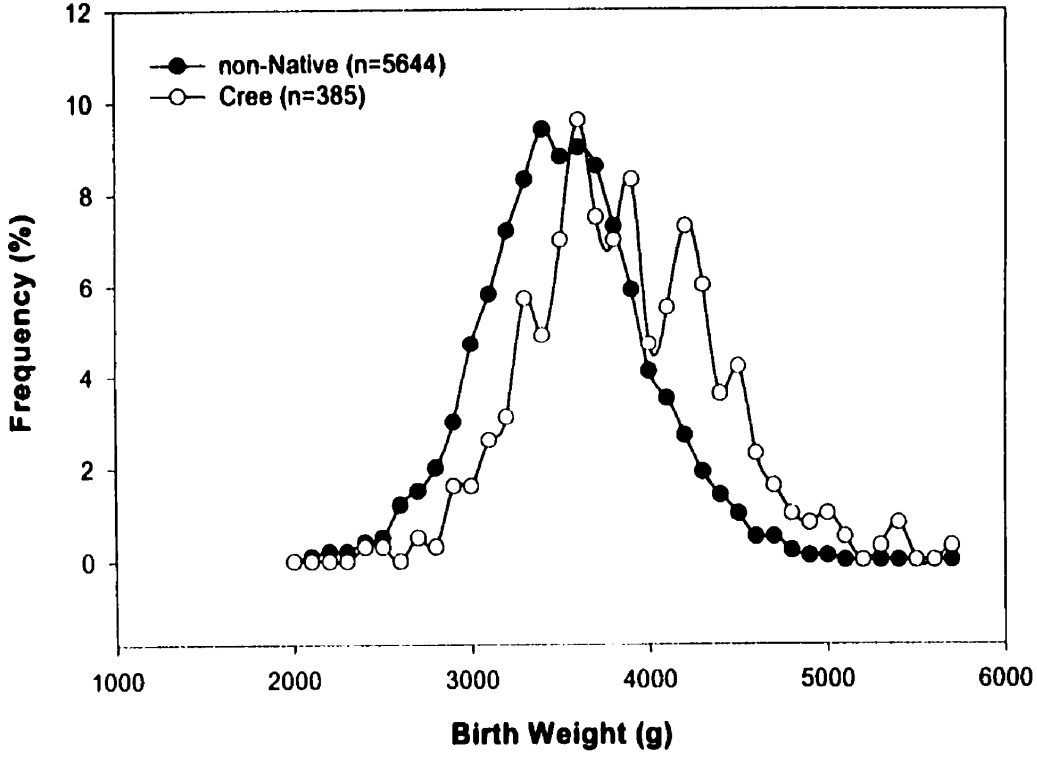
Figure 1. Birth Weight Distribution* of Cree and non-Native Infants



* Points represent 100-g birth weight intervals

Figure 2. Interaction of Ethnicity with GDM on Risk for Macrosomia

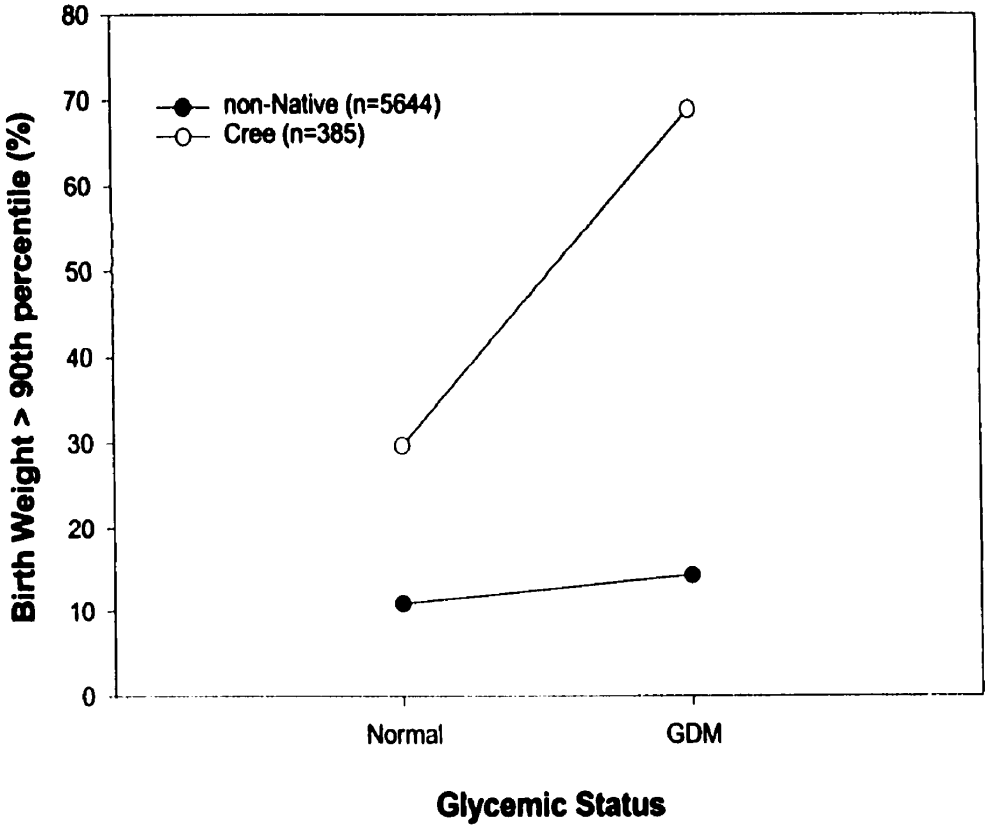


Table 1. Maternal and Infant Characteristics by Ethnicity and Percentage of Macrosomic* Infants in Each Category

	Cree				non-Natives			
Variable	N	%	% Macrosomic	P value †	N	%	% Macrosomic	P value †
Maternal age (y):								
<20	92	23.9	23.9		37	0.7	8.1	
20-25	167	43.4	35.9	0.13	689	12.2	8.0	0.02
26-30	71	18.4	36.6		2158	38.2	10.8	
30-35	38	9.9	42.1		1956	34.7	11.7	
>35	17	4.4	47.1		804	14.3	13.2	
Parity:								
≤1	221	57.4	32.6		4733	83.8	10.4	
2-4	146	37.9	37.0	0.68	890	15.8	14.6	0.001
>4	18	4.7	33.3		21	0.4	19.1	
Pregravid weight (kg):								
≤69	119	30.9	21.0		4376	77.5	9.2	
69-77	65	16.9	35.4	0.001	635	11.3	13.5	0.001
>77	201	52.2	41.8		633	11.2	21.8	

Height (cm):								
≤158	56	22.2	21.4		1077	24.8	8.4	
>158 - ≤161	46	18.3	47.8		567	13.1	7.9	
>161 - ≤164	50	19.8	30.0	0.03	726	16.7	9.6	0.001
>164 - ≤167	48	19.1	41.7		607	14.0	12.2	
> 167 - ≤170	30	11.9	36.7		893	20.6	13.6	
>170	22	8.7	54.6		468	10.8	20.1	
Body Mass Index (kg/m^2):								
≤26	72	28.6	18.1		3396	78.3	10.1	
>26-29	44	17.5	40.9	0.001	453	10.4	13.0	0.001
>29	136	53.9	44.9		489	11.3	18.6	
Total Weight Gain (kg):								
<6.8	79	20.5	32.9		285	5.1	9.5	
6.8-15.9	203	52.7	34.5	0.96	3072	54.4	8.1	0.001
>15.9	103	26.8	35.0		2287	40.5	15.4	

Glycemic Status:								
Normal	313	81.3	30.4	0.001	5330	94.5	10.9	0.17
IGT	27	7.0	22.2		41	0.7	14.6	
GDM	45	11.7	68.9		273	4.8	14.3	
Smoking:								
Yes	174	54.8	28.7	0.04	1013	82.0	7.1	0.001
No	211	45.2	38.9		4631	18.0	12.0	
Gestational age (wk):								
37	18	4.7	11.1		209	3.7	7.7	
38	47	12.2	31.9		806	14.3	8.6	
39	104	27.0	23.1	0.002	1523	30.0	9.0	0.001
40	114	29.6	39.5		1655	29.3	11.5	
41	78	20.3	48.7		1120	19.8	14.0	
≥42	24	6.2	33.3		331	5.9	17.0	
Infant Sex:								
Male	194	49.6	29.9	0.07	2885	48.9	11.5	0.31
Female	191	50.4	38.7		2759	51.1	10.7	

Type of Delivery:								
Vaginal	323	84.3	34.1	0.70	4473	79.3	10.0	0.001
Cesarean section	60	15.7	36.7		1171	20.7	15.5	

* Macrosomia was defined as birth weight >90th percentile for gestational age and sex

† P value from chi-square analyses within ethnic group

Table 2. Independent Predictors of Infant Macrosomia* among Cree and non-Native Women

Characteristic	Cree	non-Native
Maternal age (per 5 y)	1.04 (0.80-1.35)	1.15 (1.05-1.27)
Parity (primi vs. multi)	0.98 (0.57-1.71)	1.42 (1.14-1.76)
Pregravid weight (per 5 kg)	1.15 (1.07-1.23)	1.22 (1.18-1.26)
Net rate of weight gain (per 0.1 kg/wk)	1.13 (0.97-1.32)	1.35 (1.26-1.44)
Gestational diabetes (Yes/No)	4.46 (2.24-9.26)	1.15 (0.79-1.65)
Smoking (Yes/No)	0.73 (0.46-1.16)	0.51 (0.39-0.66)

* Macrosomia was defined as birth weight >90th percentile for gestational age and sex

Values are Adjusted Odds Ratios (95% Confidence Interval) from Multiple Logistic Regression Analysis

Table 3. Independent Effect of Ethnicity and Other Risk Factors for Infant Macrosomia* in Pooled Analyses of the Cree and non-Native Data

Characteristics	Adjusted Odds Ratio (95% CI)
Ethnicity (Cree vs. non-Native)	3.63 (2.69-4.90)
Maternal age (per 5 y)	1.13 (1.04-1.24)
Parity (primi vs. multi)	1.33 (1.09-1.63)
Pregravid weight (per 5 kg)	1.20 (1.17-1.25)
Net rate of weight gain (per 0.1 kg/wk)	1.32 (1.24-1.40)
Gestational diabetes (Yes/No)	1.54 (1.13-2.07)
Smoker (Yes/No)	0.56 (0.45-0.70)

* Macrosomia was defined as birth weight >90th percentile for gestational age and sex

CHAPTER 6
SUMMARY AND CONCLUSION

The main motivation for this research was the high priority for diabetes prevention assigned by the Canadian First Nations peoples, given the recent escalation in diabetes rates and associated complications among many Native populations in North America and world-wide (Harris et al 1997a, Daniel and Gamble 1995). This research addressed the paucity of information on perinatal health of indigenous peoples in Canada. Gestational diabetes mellitus (GDM) and infant macrosomia in a Canadian Native population (the James Bay Cree) were the focus of this investigation for two reasons:

a) Studies in the general population indicate a high rate of progression to Type 2 diabetes among women with GDM (Damm et al 1992, Kaufmann et al 1995, Kjos et al 1995, Peters et al 1996, Simmons 1996), and also an increased risk for adverse immediate (Hod et al 1991, Rey et al 1996, Adams et al 1998) and subsequent perinatal outcomes (Silverman et al 1991, Pettitt et al 1993, Rizzo et al 1991). Also, little information is available on the epidemiology of GDM among Canadian Native women.

b) Infant macrosomia is one of the undesirable outcomes of maternal diabetes but may also be a consequence of other maternal factors such as obesity. The Cree of James Bay have the highest reported mean birth weight world-wide but the reasons for this have not been explored.

The first study of this thesis was undertaken to estimate the prevalence of GDM among the James Bay Cree over a 2 y period (January 1995-December 1996) using standardized criteria. Results of this study indicated that Cree women had one of the highest prevalence rates of GDM reported for an Aboriginal group worldwide at 12.8%. The following reasons strengthen the accuracy of our prevalence estimate: the use of standardized criteria for GDM diagnosis, the availability of screen or diagnostic test values for 88.5% of eligible Cree women in eastern James Bay, and the use of the positive predictive value of the screen to estimate likely cases of GDM among women with a positive screen who had no or incomplete information for laboratory values on the diagnostic test. Previous studies reporting GDM prevalence in different North American Native groups may have underestimated the true prevalence due to incomplete screening

or failure to estimate cases of GDM among positive screenees who did not undergo the diagnostic test (Sugarman et al 1989, Livingston et al 1993, Benjamin et al 1993, Murphy et al 1993, Harris et al 1997b, Pettitt et al 1994, Rith-Najarian et al 1996). It is possible that the prevalence of GDM among the Cree in our study may be overestimated due to two reasons: a) inclusion of some cases of Type 1 or 2 diabetes not detected prior to pregnancy; b) exclusion of pregnancies without any screen or OGTT values from the GDM estimate (n=75). In the first instance even if cases of GDM diagnosed in the first trimester (n=6) had been regarded as cases with pregestational diabetes and excluded, the prevalence estimate of GDM would have decreased by only 1%. In the second instance if the 75 pregnancies with no screen or OGTT values were not excluded and were regarded as low risk for GDM (0 cases in 75 subjects), the prevalence estimate of GDM would decrease only by 1.5%. However, from our data it appears that age, parity and pregravid body weight were not different between women screened and those not screened, decreasing the likelihood that non-screenees were more or less susceptible to GDM than screenees.

The second study of this thesis had dual objectives. The first was to identify independent determinants of GDM among the Cree. Specifically, the risk for GDM imparted by age, parity, body weight, height, previous GDM, prediagnostic rate of weight gain, smoking status, total energy intake, dietary macronutrients and physical activity prior to GDM diagnosis were determined in multivariate analyses. The second objective was to determine whether Cree women were at an elevated risk for GDM compared with non-Native women after accounting for differences in the distributions of major risk factors. Two approaches were used to control for these differences. The first approach involved statistical adjustment for the differences and the second method included frequency matching of Cree women with non-Native women for age and body weight. Independent risk factors of GDM among the Cree were advanced age, pregravid overweight and previous GDM and were similar to those reported among women in the general North American population (Dooley et al 1991, Berkowitz et al 1992, Dornhorst et al 1992, Solomon et al 1997). In addition, low energy intake was also an independent risk factor and may be a marker for low physical activity among Cree women. A comparison of risk for GDM between Cree and non-Native women revealed an

interaction between ethnicity and pregravid weight. Only overweight Cree women were at an increased risk for GDM compared with overweight non-Native women. This is the first study to report an interaction between ethnicity and body weight as a determinant of GDM.

In the final study, a similar analytical framework was used to identify independent risk factors for infant macrosomia among the Cree and compare these with non-Native Canadian women. Our study confirmed that Cree infants indeed have one of the highest mean birth weight (3859 ± 519 g) and macrosomia prevalence (34.3%) reported in the world. An analysis of the effects of age, parity, pregravid weight, height, gestational weight gain, GDM, smoking status, dietary intake of total energy and macronutrients and physical activity during pregnancy on risk for infant macrosomia revealed pregravid weight, height and GDM as the only important risk factors among the Cree. When these were compared to risk factors among the non-Natives, an important difference was noted between Cree and non-Native women with regard to the impact of GDM on infant macrosomia. While GDM increased the risk for macrosomia 4.5-fold among the Cree, it had no effect among the non-Natives. Reports from several well-controlled studies on the effects of GDM on macrosomia are equivocal; some report no differences in rates of macrosomia between women with vs. without GDM (Okun et al 1997, Maresh et al 1989) while others report higher rates of macrosomia among women with GDM (Jang et al 1997, Di Cianni et al 1996, Casey et al 1997). A likely explanation for differences across studies may be due to differences in stringency of glycemic control among women with GDM. The differential effect of GDM on macrosomia between Cree and non-Native women in our study may similarly reflect differences in the severity of hyperglycemia between Cree and non-Native women and/or differences in treatment modalities. This finding underscores the need to carefully evaluate existing treatment strategies for GDM among Cree women and optimize their glycemic levels in order to minimize the risk for infant macrosomia.

Cree infants were heavier than non-Native infants by 235 g even after statistically adjusting for differences in the distribution of risk factors for macrosomia between the two populations including GDM prevalence. This may reflect genetic differences in fetal growth. It is uncertain whether the high rate of macrosomia among the Cree is harmful.

Cesarean section rates were not elevated among Cree women compared with non-Native women and were not associated with macrosomia among Cree women. Other potential adverse outcomes associated with macrosomia were not evaluated in this study.

In conclusion, this research has made a significant contribution to the existing Aboriginal literature by documenting the epidemiology of diabetes and infant macrosomia among the Cree of James Bay and providing insight into ethnic differences in GDM and macrosomia risk. Our documentation of a high prevalence of GDM among the Cree, the increased risk for GDM only among overweight Cree women and the exaggerated risk for macrosomia among Cree women with GDM, have important implications. They underscore the need to target pregravid overweight for GDM prevention among the Cree through culturally acceptable interventions including dietary modification and ways of increasing physical activity. Also, existing treatment strategies for GDM among Cree women need to be reexamined in light of the evidence that risk for infant macrosomia is greatly elevated among Cree women with GDM. Finally, this research has raised important questions, which can serve as a basis for future studies among the Cree. Specifically, the reasons why overweight Cree women are at an increased risk for GDM compared with overweight non-Native women remain to be determined. Potential reasons could be differences in diet, physical activity, percent body fat, or fat distribution and need to be examined in future well-controlled studies. Also, whether the increased prevalence of macrosomia among the Cree has any deleterious consequences in the short- or long-term remains to be determined.

6.1 References

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