Nutritional Predictors of Infant Birthweight in Gestational Diabetes

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Abstract

Nutritional Predictors of Infant Birthweight in Gestational Diabetes Mellitus (GDM)

The predictors of birthweight (BWT) in normal pregnancy are well established. The objectives of this study were to characterize and determine predictors of BWT among women diagnosed with GDM. A cohort of 436 GDM full-term pregnancies (followed 1978 1989) were examined using data abstracted from the Royal Victoria Hospital Antenatal Diabetic Clinic charts and McGill Obstetric and Neonatal Database. Women were treated with insulin and/or diet. Dietary treatment (mean 2047 kcal/d) significantly decreased the rate of weight gain and mean fasting plasma glucose (FPG). Regression analysis identified several predictors of BWT (mean 3520 g): prepregnancy body mass, height, smoking, pre-diagnostic rate of weight gain, FPG, gestational age, infant gender, and length of treatment. Stratification by body mass indicated that among non-obese women with GDM, FPG and length of treatment were not significant predictors of BWT. In conclusion, since women with normal pregravid mass and prediagnostic weight gain are at lower risk of high BWT, these require consideration, in addition to plasma glucose criteria, when treating GDM.

Résumé

Les Prédicteurs Nutritionnels du Poids des Nouveaux-nés dans le Diabète Gestationnel (DG)

Les facteurs permettant de prédire le poids de l'enfant à la naissance sont clairement définis pour la grossesse. L'objectif de cette étude était d'identifier les prédicteurs du poids des nouveaux-nés chez les femmes souffrant de diabète gestationnel. Les dossiers de 436 femmes diabétiques ayant eu une grossesse à terme (suivies de 1978-1989) sélectionnés parmi ceux de la clinique de diabète prénatale de l'hopital Royal-Victoria et ceux de la banque de données en obstétrique et néonatalité de l'Université McGill ont été analysés dans cette étude. L'insuline et/ou la diète ont été les traitements utilisés pour assurer une grossesse normale chez ces femmes diabétiques. Le régime alimentaire (2047 Kcal/jour en moyenne) a été associé à des baisses significatives du gain de poids et de la glycémie des femmes suivies. L'analyse de régression a permis d'identifier les prédicteurs du poids des nouveaux-nés (3520 g) suivants: l'indice de masse corporelle de la mère avant la conception, la taille, l'usage du tabac, le gain de poids avant diagnostique de diabète, la glycémie, la durée de gestation, le sexe de l'enfant et la durée du traitement. Par contre, l'analyse des données en fonction de la masse corporelle des femmes indique que la glycémie et la durée du traitement ne sont plus de bons prédicteurs du poids du nouveau-né chez les femmes diabétiques de poids normal. En conclusion, cette étude démontre qu'il faut considérer le poids pré-gravide des femmes et le gain de poids précédant le diabète en plus du contrôle de la glycémie lors du diabète gestationnel, puisque ces variables sont associées à un moindre risque de surpoids des nouveaux-nés.

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A. Introduction

In normal pregnancy many variables have been identified as predictors of intrauterine growth and subsequent birthweight, including pregravid weight, weight gain and energy intake (Kramer 1987). Research related to factors influencing infant birthweight in gestational diabetic pregnancy is limited primarily to the use of insulin and plasma glucose control, and more recently to maternal obesity. Maternal obesity may reflect an obese pregravid weight or excessive gestational weight gain or both. To date no comprehensive statistical analysis has examined these factors in association with the important confounding variables in gestational diabetes mellitus (GDM). The need to identify independent predictors of birthweight in this high-risk population and increase understanding of weight gain and glycemic control in obese and non-obese gestational diabetes is important for the optimal management of GDM.

B. Overview of Gestational Diabetes Mellitus

B.1 Definition of Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) is defined as "glucose intolerance of variable severity with onset or recognition in present pregnancy" (National Diabetes Data Group [NDDG] 1979). This definition applies regardless of whether or not insulin therapy is required or the diabetes persists after pregnancy; it does not remove the possibility that carbohydrate intolerance may have existed prior to pregnancy (American Diabetes Association 1985).

B.2 Epidemiology of GDM

Reports of pregnancies affected by GDM vary from < 1 to 12% (Sepe et al 1985, Hadden 1985), although many believe that the true prevalence lies between 1 and 5% (O'Sullivan and Mahan 1964, Hollander 1988, Vaughan and Oakley 1986). Reasons for these

discrepancies have been postulated in two main areas. Firstly, there are known predictors of GDM, including age, height, weight, race and parity, that influence prevalence and vary from one population to another. The associations which may exist between these determinants, for example between race and stature (Green et al 1990) have not been explored and may lead to pockets of high incidence. Secondly, much controversy exists in the approaches to screening and definitions for diagnosis vary considerably (Hadden 1985).

Women who develop GDM are significantly older, heavier, shorter and more parous than non-diabetic controls (Al-Shawaf et al 1988, Sepe et al 1985, Jacobson et al 1989, Maresh et al 1989). Green et al (1990) examined the ethnic variation of GDM in 3336 women in a universal screening program and found a significantly higher prevalence among Chinese (7.3%) and Hispanic (4.2%) women than in black (1.7%) and non-Hispanic white (1 6%), after controlling for age, height and weight Diagnosis of GDM was also high in the Filipina, Pacific Islander and Middle Eastern women, but the sample size of these groups was not large enough to draw conclusions. O'Sullivan and Mahan (1964) established an incidence of 2% and reported no difference in incidence between the 60% non-Hispanic white and 40% black urban population which they studied Pettit and coworkers (1980) studied the Pima Indians, who have an incidence of GDM nearly 40 times that of the population described by O'Sullivan and Mahan (1964). Massion et al (1987) found 6.1% of the Navajo Indians (Arizona) to have GDM.

Another factor which influences the appearance of GDM is a past history of GDM. Reports of GDM recurring in subsequent pregnancies range from 60% (Philipson and Super 1989) to 90% (Hollander 1988) of women.

The problems of ascertaining the true prevalence of GDM have been discussed at length in the literature (Sepe et al 1985, Green et al 1990, Hadden et al 1985, Hunter and Keirse 1989, Ales et al 1989). Since universal screening for GDM, as recommended (ADA 1985), is not practiced ubiquitously many studies introduce a selection bias through the inclusion of only high-risk patients, not representative of the population (Green et al 1990). The most predominant concern however is the international disagreement on the most appropriate diagnostic criteria for diabetes in pregnancy. The criteria for GDM screening

and diagnostic tests will be expanded upon in the next section.

B.3 Screening and Diagnosis

In the past, women have been identified as candidates for the glucose screening test for GDM on the basis of the physicians' identification of risk factors and markers which include: family history of diabetes in a first degree relative, previous stillbirth or spontaneous miscarriage, maternal obesity, advanced maternal age, a parity of 5 or more, a past history of GDM, or a large-for-gestational-age fetus, glucosuria, polyuria, polydipsia, (Hollander 1988, Hollingsworth 1985, Blumenthal et al 1987). However, many studies have shown that only one-third to one-half of gestational diabetics will be detected if screening is done on the basis of risk factors alone (Massion et al. 1987, Lavin 1985). Consequently the American Diabetes Association (ADA 1985) recommends universal screening of all pregnant women between the 24th and 28th week of gestation for the detection of abnormal carbohydrate tolerance. Implementation of the recommendation for universal screening of pregnant women varies among physicians. Indeed some practitioners are against sending all their patients for a glucose screening test and argue that evidence supporting this practice is weak (Ales et al. 1989, Hunter and Keirse 1989).

The glucose screening test (GST) involves ingesting a 50-gram carbohydrate load at any time during the day and measuring the plasma glucose level one hour later. A value greater than or equal to 7.8 mmol/L (140 mg/dL) indicates the need for the full diagnostic test, known as the oral glucose tolerance test (OGTT) (ADA 1985). After studying the GST results of gestational diabetics and non-diabetics, which were taken on two consecutive days, Sacks et al. (1989) suggested that women with values greater than 5.3mmol/L (95mg/dL) should be tested again, particularly if risk factors are present.

The OGTT requires three days of unrestricted diet (with a minimum of 150 g of carbohydrate per day) followed by an overnight fast, and is then performed by the administration of a 100-gram glucose load. Plasma glucose is measured at fasting, one, two, and three hours post-glucose administration, and should be less than the OGTT values shown below (ADA 1985), according to the National Diabetes Diagnostic Group (NDDG), who adapted them from the criteria of O'Sullivan and Mahan (1964).

Time	Plasma Glucose Value
Fasting	5.8 mmol/L (105 mg/dL)
One hour	10.6 mmol/L (190 mg/dL)
Two hour	9.2 mmol/L (165 mg/dL)
Three hour	8.1 mmol/L (145 mg/dL)

If two or more of these levels are reached or exceeded definitive diagnosis is made and the patient is usually referred to an antenatal diabetic clinic for intensive treatment and follow-up. There are practitioners who advocate that women with one abnormal OGTT value (Langer, Anayaegbunam, et al 1989) or a normal OGTT after an abnormal glucose screen (Tallarigo et al 1986) are at an elevated risk of adverse perinatal outcome, and therefore would benefit from a diabetic regimen as well.

Criteria for diagnosis have also been developed by the NIH-NDDG, the WHO, the European Association for the Study of Diabetes, all of which have been described elsewhere (Evans et al 1987, Harris 1988). Many European countries, however continue to use the World Health Organization (WHO) criteria which involves a 75-gram glucose loading test for both pregnant and non-pregnant individuals, while most North American centres use the 100-gram glucose load values developed by O'Sullivan and Mahan (1964). At the Second International Workshop-Conference on GDM held in 1985, consensus was reached to adapt the criteria of O'Sullivan and Mahan (ADA 1985). Although the O'Sullivan and Mahan study (1964) is used in North America, it has been criticized for many weaknesses and these will be discussed below.

O'Sullivan and Mahan aimed to define abnormal gestational glucose tolerance when they tested women, with the 3 hour glucose tolerance test described earlier, in their second and third trimester of pregnancy during the mid 1950's; they followed them by testing them annually for eight years to determine who developed Type II diabetes. Of the cohort who developed diabetes mellitus, 40% had 2 OGTT values 3 standard deviations above the mean, and 16% had 2 values 2 SD above the mean. These authors subsequently decided that 2 values 2 SD above the mean would catch the majority with abnormal glucose tolerance.

Thus the origin of the abnormal OGTT is based on the appearance of subsequent diabetes, that is after pregnancy, not on the presence of GDM; therefore the diagnosis of

GDM was not based on a glucose tolerance level at which adverse pregnancy outcomes were observed (Hunter and Keirse 1989). Secondly the glucose levels were originally measured in whole blood using the outdated Somogyi-Nelson method. Since plasma is now the preferred medium for measuring glucose, the NDDG (1979) attempted to convert the whole blood values to plasma values by applying a conversion factor of 15% (Schwartz and Brenner 1982). Naylor (1989) pointed out that due to rounding off of the converted numbers, the new criteria ranged from 13.8% to 16.7% above the original whole blood values. As well the conversion factor is likely invalid for pregnancy given the physiological fall in hematocrit during gestation as blood volume increases 50%. Another drawback with the test is it's reproducibility which Harlass et al. (1991) demonstrated was 78% of the time and recommended that the test be repeated when the 1-hour value is abnormal or when the first three values are near the upper end of the normal range.

Although the screening and diagnostic criteria are not perfect, adequate consensus has been reached in North America to continue to employ them until a better option is determined. There has been some discussion (ADA 1985) about a 75 g glucose load test to replace both the screening and the diagnostic test. However since much controversy still exists as to the actual criteria of glycemic levels that demarcate GDM, further research in this area is needed.

B.4 Physiology of GDM

Pregnancy has often been referred to as a diabetogenic state due to altered metabolism which may manifest as varying degrees of carbohydrate intolerance in the latter half of gestation (Vaughan et al 1986). Early in normal pregnancy the rising estrogen and progesterone levels stimulate beta-cell hyperplasia and consequently increase insulin release. Fasting plasma glucose (FPG) drops approximately 10% by mid to late first trimester, as peripheral glucose utilization is enhanced (Hollingsworth 1985). The fetal drain on maternal glucose at this stage in pregnancy can account for only part of this reduced FPG; much of the glucose is being used for maternal glycogen storage. Lipid storage is also predominant during the first half of pregnancy, since the hormonal changes also stimulate fat synthesis and fat cell hypertrophy, and inhibit lipolysis (Hollingsworth

1985). These anabolic changes in metabolism result in significant maternal energy storage over the first twenty weeks of gestation.

In the second half of normal pregnancy, the increasing placental production of human chorionic somatomammotropin (hCS), as well as other hormones (prolactin, cortisol and glucagon) cause the catabolism of glycogen and lipid stores. These hormonal changes also create a moderate, but normal amount of insulin resistance, such that more insulin is required to maintain euglycemia. Insulin production increases in tandem with the growth of the conceptus. The metabolic responses before and after meals are exaggerated compared to the non-gravid state, and are referred to as accelerated starvation and facilitated anabolism respectively (Freinkel 1980, Buchanan et al 1985). If hCS cannot stimulate adequate insulin release, or when the maternal system has insufficient insulin reserves, impaired glucose tolerance will result (Hollingsworth 1985). The degree of carbohydrate intolerance depends on the extent to which the beta-cells satisfy the need for insulin.

If glucose intolerance is diagnosed during pregnancy, the oscillating insulin and nutrient responses pre- and post-prandially require consideration for management strategies. In the fasted state, the fetus continues to draw on the maternal circulating glucose and gluconeogenic substrates; as blood glucose drops the maternal system is stimulated to mobilize lipid stores for energy, and this results in increased plasma nonesterified fatty acids and ketone bodies (Evans et al 1987, Vaughan et al 1986). In the fed state maternal plasma glucose, amino acids and fatty acids rise above normal postprandial levels, providing a surplus of fuels to the fetus.

B.5 Management of GDM

The alteration in pathophysiology of the woman who develops GDM provide the basis for therapeutic approaches. The goals of GDM management are: to normalize metabolism as much as possible; and to provide adequate, but not excessive nutrition to the mother and fetus, and hence to optimize neonatal outcome. These goals are achieved at many centres by intensive antepartum monitoring of mother and fetus, in combination with diet and possibly insulin therapy.

B.5.1 Monitoring

Intensive monitoring involves three fundamental components: strict metabolic control (daily measures of urinary glucose and ketones, weekly measures of fasting and post-prandial plasma glucose); frequent antepartum maternal and fetal surveillance (weekly fetal monitoring with non-stress test, ultrasound intermittently to assess fetal growth, amniotic fluid status and any developmental abnormalities); and a team approach toward patient care (evaluation and follow-up by a nurse, dietitian, perinatologist and endocrinologist) (Buchanan et al 1985, Hollander 1988). Indeed the intensity of such protocols varies between health centres.

B.5.2 Diet Therapy

The underlying premise of diet therapy has been aimed at glycemic control through regulation of quantity and quality of carbohydrate intake. Some authors suggest that not less than 200 g of carbohydrate is distributed over 3 meals and 2 to 3 snacks, while avoidance of simple carbohydrates is encouraged (Hollander 1988, Vaughan and Oakley 1986, Buchanan et al 1985). Breakfast should be small in volume and low in carbohydrate since early morning glucose intolerance is severe (Hollander 1988). The guidelines for energy intake during normal pregnancy are well established (Health and Welfare 1987), however there is little consensus on requirements for the gestational diabetic pregnancy. The Jovanovic Approach (Jovanovic and Peterson 1980) was developed for insulin-dependent diabetics who become pregnant and it has been adapted for the GDM population by some centers, including the clinic which this study represents; it suggests the distribution of carbohydrate and energy by a pattern of fractions of 18, as shown below.

Time	Meal	Fraction of daily requirement
8:00 am	Breakfast	2/18
10:30 am	Snack	1/18
12:00 pm	Lunch	5/18
3:00 pm	Snack	2/18
5:00 pm	Supper	5/18
8:00 pm	Snack	2/18
11:00 pm	Snack	1/18

Prescibed energy levels based on ideal body weight have been reported from a minimum of 25 kcal/kg (Jacobson et al 1989) to a maximum of 38 kcal/kg (Buchanan et al 1985, Vaughan et al 1986). Energy levels have also been prescribed based on actual body weight of women with GDM, such as 25 kcal/kg for obese (Algert et al 1985) and 36 kcal/kg for lean (Langer et al 1989). Adashi and co-workers (1979) instruct 1800 calories initially with an increment only if ketonuria is present. Maresh and colleagues (1989) reported diets of only 1500 calories for their obese patients and 1800 for their non-obese gestational diabetics. Many authors have suggested that energy restricted diets may be appproprnate for obese GDM (Hollander 1988, Buchanan et al. 1990), but concern about the ketogenic effects of such restrictions has hampered commitment to this recommendation by most (Edwards et al. 1978, ADA 1985, Vaughn and Oakley 1986).

Some studies mention that a diet was instructed by the clinic dietitian, however only a few describe the composition and timing of the actual diet consumed, and how dietary compliance was measured, if at all. Lack of rigour in this area of diabetic management may account for the absence of well-designed research which evaluates the impact that diet therapy during GDM may have on pregnancy outcome, particularly birthweight.

B.5.3 Maternal weight gain

Restrictions on maternal weight gain during normal pregnancy has been associated with an increased risk of low birthweight and neurological impairment (Singer, 1968) prompting the Committee on Maternal Nutrition of the National Academy of Sciences to increase the weight gain recommendation for normal pregnancies to 10 to 13 kg. Since 1971, physicians have been warned that limiting a mother's gestational weight gain may be dangerous to the fetus. The clinical application of these recommendations to the gestational diabetic is confusing.

Numerous antenatal diabetic centres claim to encourage the continuance of normal weight gain, but rarely report on the post-diagnostic weight changes which are likely to result from diets for diabetes of restricted energy levels. Hollander (1988) reported that the extreme energy restrictions implemented at her clinic for GDM resulted in many patients failing to achieve adequate weight gain for 1 to 2 weeks after commencing treatment. Some

recommended absolutely no weight gain (Maresh et al. 1989,) while others demonstrated that energy restriction for glycemic control and/or the prevention of large-for-gestational-age babies, can lead to small-for-gestational-age babies (Langer et al 1989) in the gestational diabetic.The rate of weight gain post-diagnosis has received little attention as a management strategy for the control of fetal growth, although many studies have recognized that an excessive rate of maternal weight gain likely contributes significantly to the development of large babies of women with GDM.

B.5.4 Insulin Therapy

Many centres employ the recommendations of the Second International Workshop-Conference on Gestational Diabetes Mellitus which indicates the initiation of insulin therapy for the GDM when fasting plasma glucose (FPG) levels are consistently ≥ 5.8 mmol/L (105mg/dL) or when the 2 hour postprandial plasma glucose (PG) is ≥ 6.7 mmol/L (120 mg/dL) (ADA 1985). Some studies reported stricter criteria for insulin therapy, with FPG > 5.3 (95 mg/dL) (Langer, Anyaegbunam et al 1989), while others have more lax values of FPG > 6.0 (108 mg/dL) (Maresh et al. 1989). Roversi et al. (1979) employed a protocol of giving all GDM patients the maximum tolerated dose of insulin until signs of hypoglycemia appeared.

Controversy persists over the use of prophylactic insulin therapy for all GDM to reduce neonatal morbidity, particularly the morbidity believed to be associated with macrosomic (≥4000g) infants (Coustan and Lewis 1978, Coustan and Imrah 1984, Leikan et al 1987, Thompson et al 1990). However as Kalkhoff (1985) discussed, before practices such as prophylactic insulin are implemented, the role of diet, maternal obesity, and weight gain during pregnancy need to be evaluated in research which simultaneously examines the effects of insulin and diet therapy on pregnancy outcome.

C. Consequences of Gestational Diabetes Mellitus

The purpose of screening, diagnosing and treating patients for GDM is ultimately to reduce the incidence of perinatal morbidity and mortality. The most frequent adverse outcome of

GDM is believed to be macrosomia, or excessive growth resulting in a birthweight of 4000 grams or more (Drexel et al. 1988, Philipson et al. 1989). However other outcomes of concern include congenital anomalies; birth trauma for the mother and infant (Coustan and Imrah 1984); neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia; and respiratory distress syndrome (Jacobson et al. 1989, Maresh et al. 1989). The consequences of GDM for the fetus, neonate and mother will be discussed.

C.1 Fetal Consequences

Intrauterine growth in GDM is thought to be affected by abnormal levels of nutrients The Pedersen hypothesis (Pedersen 1954) of macrosomic growth late in pregnancy proposes that maternal hyperglycemia, due to poorly controlled GDM, leads to fetal hyperglycemia which trigger fetal beta-cell hyperplasia, since maternal insulin cannot cross the placenta to the fetus. Subsequent fetal hyperinsulinism causes increased glucose utilization, which results in excessive fetal growth (Evans et al 1987). Freinkel (1980) modified Pedersen's hypothesis to include the contribution of excess amino acids and lipids, as well as glucose, to the fetal growth in GDM, which accelerates beyond the normal rate. Hollingsworth (1985) suggested that even the mildest form of GDM gives rise to above normal circulating levels of glucose, proteins and lipids, which are transported to the fetus and may contribute to accelerated growth.

Among poorly-controlled pregestational insulin-dependent diabetics, congenital malformations can occur during embryogenesis, which is complete by week 7 of gestation; possibly due to the teratogenic effect of glucose and/or ketones, but not insulin, (Blumenthal et al 1987). There is little agreement on the prevalence of congenital defects among infants born to GDM mothers; many researchers argue that GDM does not manifest until the late second or early third trimester and hence congenital anomalies are not a significant phenomena; while others claim that early metabolic disturbances of GDM cause an elevated incidence. Some have reported the rates of congenital anomalies to be elevated (Tallarigo et al. 1986, Molsted-Pedersen et al. 1980, Lavin et al. 1983) and in some studies

rates were not dissimilar to rates of congenital malformations among insulin dependent diabetics (Plehwe et al 1984) Chung and Myrianthopoulous (1975) showed in a well-designed study that there is not an elevated risk of congenital anomaly in GDM; a finding that was supported by a recent prospective study (Jacobsen et al. 1989) and others (Al-Shawaf et al. 1988, Sepe et al. 1985). In fact, Sepe (1985) found GDM to be a protective factor for anomalies.

In the fasting state a gestational diabetic is more prone to ketosis than a normal pregnant or non-pregnant woman. Ketone bodies arise from lipid catabolism and readily cross the placenta to be used by the fetus as an oxidative fuel (Leturque et al. 1989, Adam et al. 1975). Many still hold the belief that fetal exposure to ketone bodies during gestation can impair intellectual development of the infant (Freinkel 1980, Rizzo et al. 1991) . The original evidence of this effect from the renowned study of Churchill and Berendes (1969) is unsubstantiated and disputed by others (Naeye and Chez 1981). Evidence suggests that ketosis may be harmful during organogenesis (Freinkel et al. 1986), but not counterproductive to fetal growth and development in the third trimester (Robinson et al. 1980, Shambaugh 1985). There is a lack of well-designed long-term studies to assess the impact of gestational ketosis on the child of the (gestational) diabetic.

Severe GDM may appear in the first half of pregnancy and require insulin therapy immediately; it is believed that this form may represent the manifestation of pre-existing diabetes since it heightens the risks of consequences for the fetus. These consequences include intrauterine fetal death, which may be caused by ketoacidosis unless treated promptly; fetal hypoglycemia, related to fetal hyperinsulinism or maternal hypoglycemia; and placental insufficiency (Buchanan et al. 1985, Blumenthal and Abdul-Karim 1987).

C.2 Neonatal Consequences

Neonatal consequences are less evident than once thought, possibly due to better treatment or the inclusion and follow-up of less severe GDM. Many studies have reported that GDM pregnancies have a significant increase in incidence of macrosomia, defined as birth weight $\geq$ 4000 g and of large-for-gestational-age, defined as LGA ie $\geq$ 90th percentile infants (Maresh et al. 1989, Langer et al. 1986, Jacobson et al. 1989). A study by Philipson and

coworkers (1989) indicated that women with GDM have heavier infants, but without significant morbidity; in addition they reported that macrosomia was significantly associated with older, obese women whose GDM was treated with insulin

The concern over higher birthweight is the greater risk of birth trauma and related complications. However the association between excess morbidity and birthweight does not appear until birthweights reach 4500 g (Ales and Santini 1989) Spellacy et al (1985) reported only 5% of infants with birthweight over 4500 g were born to GDM, while the background incidence (among women without GDM) of infants over 4500 g is 1.7% Although macrosomia is believed to be the hallmark of GDM, GDM occurs less frequently than other factors found to be predictors of macrosomia (Boyd et al. 1983). These factors include high prepregnancy weight, excessive weight gain and postterm dates (Boyd et al. 1983, Spellacy et al. 1985).

Shoulder dystocia may result from macrosomia and cause fractured bones or peripheral nerve damage such as Erb's Palsy. Reports of incidence in the general population range between 0.3% (Al-Najashi et al. 1989, Acker et al. 1985) and 1.3% (Cyr et al. 1984), while in the GDM population estimates of shoulder dystocia have been reported from 0% (Jacobsen et al. 1989) to 15.7% (Al Najashi et al. 1989). Keller and colleagues (1991) recently reported that class A2 GDM (insulin-treated) did not have an increased the risk of dystocia and that almost one-half of the occurences were in infants <4000 g.

Maternal hyperglycemia at term triggers fetal hyperinulinism which persists postnatally; subsequently glucose utilization exceeds hepatic gluconeogenesis. In the immediate postnatal period, high plasma insulin will suppress hepatic production of glucose and the neonate may develop hypoglycemia. Although hypoglycemia is commonly named as a condition frequently occurring among infants born to GDM mothers many studies have failed to find that it occurs at significant levels (Philipson et al. 1989, Drexel et al. 1988), but some studies found significantly more hypoglycemia among GDM compared to non-diabetic controls (Jacobson and Cousins 1989).

Hypocalcemia and hyperbilirubinemia are manifestations of immature organ function. There is a lower occurence when the infant is delivered after 37 weeks

(Blumenthal 1987). Hunter and Keirse (1989) provided a critique of 4 studies comparing incidence of neonatal jaundice in GDM and non-GDM and concluded that there is no evidence that infants of mothers with GDM are at increased risk

Respiratory distress syndrome does not occur more often in infants of GDM mothers (Philipson et al 1989), nor has neonatal mortality been reported more frequently in GDM (Forsbach et al 1988, Drexel et al. 1988).

In summary, the consequences of GDM for the neonate seem equivocal and may be significant only when birthweight is 4500 g or more.

C.3 Maternal Consequences

In a prospective population-based study Jacobson and Cousins (1989) compared maternal (and infant) outcomes in GDM with non-diabetic controls; they found an increase in polyhydramnios and infectious complications related to repeat cesaerean section, but no other differences in frequency of pregnancy-induced hypertension, dystocia, preterm labor or pyelonephritis. In a comprehensive critique of the GDM literature Ales and Santini (1989) reported that the research to date has not shown that a woman with GDM is at increased risk of morbidity.

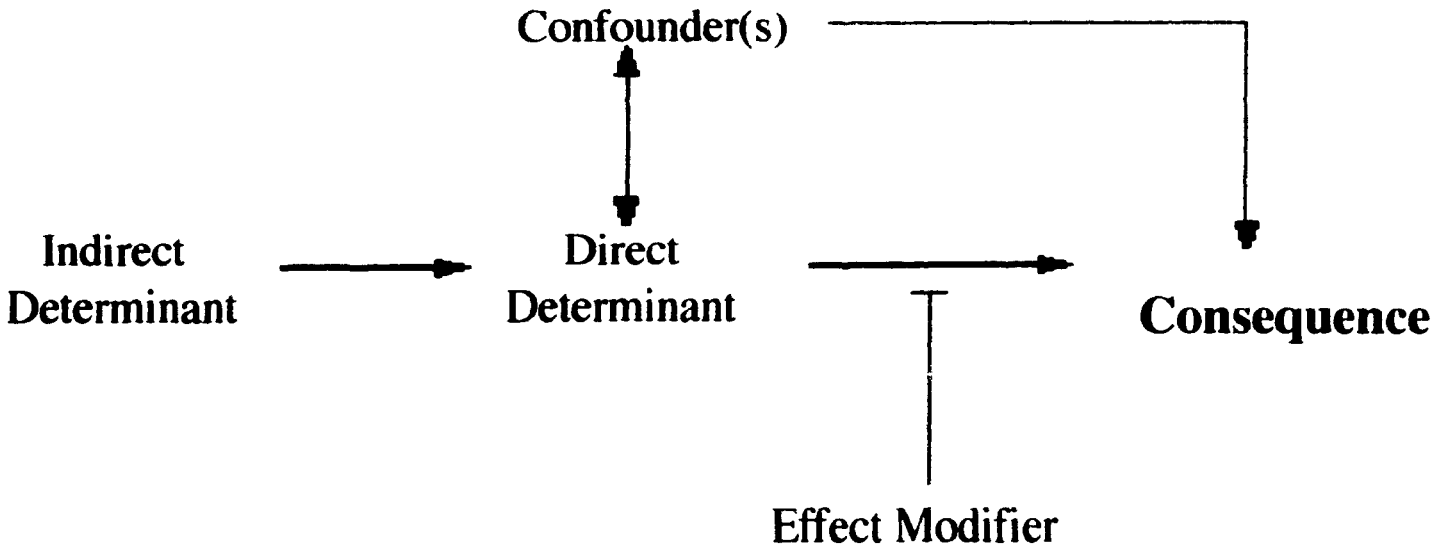
D. Predictors of Infant Birth Weight

D.1 Introduction

Intrauterine growth is affected by a multitude of factors, many of which have been well researched in normal pregnancy. When assessing the effect of an independent variable on a dependent variable, such as maternal weight gain on infant birth weight, it is important to consider all other variables which could affect this relationship. A hypothetical causal path, as shown in Figure 1 (adapted from IOM 1990), could be used to illustrate the epidemiological concepts involved.

Determinants or predictors are defined as the etiologic factors in the causal path

Figure 1. Causal path of health outcomes



(IOM 1990) and may either indirectly or directly cause the outcome or consequence. Health outcomes are often multifactorial in nature, such as infant birth weight which is affected by many nutritional (maternal weight, diet) and non-nutritional (race, infant sex, smoking) variables. Confounders may positively or negatively influence the effect of the determinant on the consequence (Last 1988), and these variables must be a determinant of the outcome, be associated (without implying causality or directionality) with the determinant, and not lie on the causal path (IOM 1990). Confounders need to be controlled for in the statistical analyses in order to obtain an undistorted estimate of the effect. Effect modifiers are similiar to confounders in that they modify the effect of an exposure or determinant on an outcome by increasing or decreasing it; however they do not need to be associated with the exposure. When applied to the issues surrounding weight gain and birth weight in gestational diabetes, the causal path may be illustrated as shown in Figure 2.

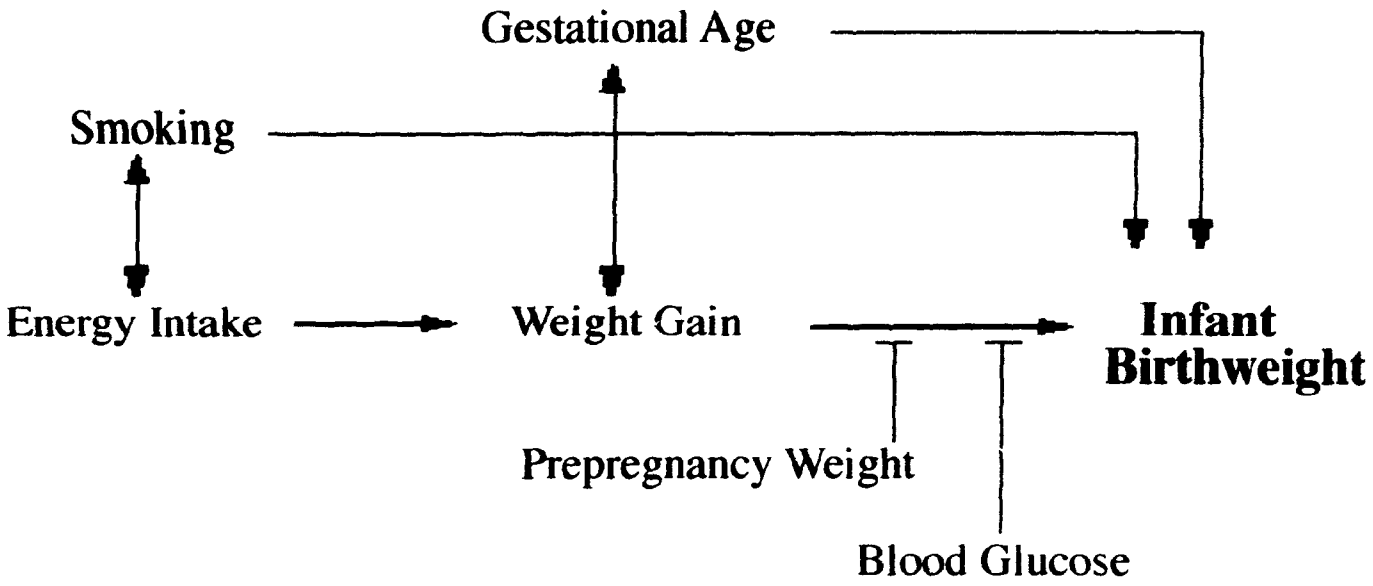
In a recent paper, Kramer (1987) discussed the findings of a methodological assessment and meta-analysis of almost 900 articles which studied birth weight. Forty-three potential determinants were identified and assessed for the existence and magnitude of effect on birth weight, in either a positive or a negative direction. The predictors of infant birth weight which Kramer (1987) established as having a causal effect on infant birth weight in normal pregnancy are listed below.

Predictors which have a causal effect on birthweight

pregravid weight	cigarette smoking
maternal height	socioeconomic status
maternal birthweight	racial/ethnic origin
maternal weight gain	episodic illness
maternal age	prior low birthweight infant
parity	infant sex

For example, women of greater stature have heavier infants. Women who had a low birth weight themselves have lighter infants. Also male infants have higher birth weight and a lower risk of intrauterine growth retardation. A number of these maternal variables are so well understood that their effect on birth weight can be calculated in increments per unit.

Figure 2. Hypothetical causal path for birthweight in GDM



Maternal variable	Increment of birthweight per unit
Weight gain (kg)	+ 21 grams
Pregravid weight (kg)	+ 9.5 grams
Maternal Height (cm)	+ 7.8 grams
Multiparity (multi vs primi)	+ 82.7 grams
Smoking (cig/day)	- 12 grams

As listed above, a well-nourished woman with an uncomplicated pregnancy will increase birthweight by about 21 grams for each kilogram of weight she gains (Kramer 1987, Anderson 1984, Rush 1970). As well, cigarettes have a negative effect: for every cigarette smoked per day throughout pregnancy there is a decrement in birth weight of about 12 grams. Thus a woman who smokes a pack of cigarettes per day will deliver an infant (25 cig x 12 g) 300 grams lighter than if she hadn't smoked, everything being equal (Kramer 1987). These predictors apply to singleton pregnancies free of complicating conditions such as diabetes mellitus.

D.2 Nutritional Predictors of Infant Birthweight

D.2.1 Weight gain

Infant birthweight is the major indicator of perinatal morbidity and mortality, and gestational weight gain is the primary predictor of infant birthweight (Williams et al. 1982). It was the high rate of low birthweight and associated perinatal loss prior to 1970, which prompted the Committee on Maternal Nutrition of the National Academy of Sciences to increase the weight gain recommendations for normal pregnancies (Committee on Maternal Nutrition 1970). After 1971, physicians were advised to counsel their patients to "eat to appetite" and gain at least 24 pounds (11 kg). These recommendations applied regardless of prepregnancy weight status; so the question remained: was a gestational weight gain of 24 pounds appropriate for overweight and underweight women?

It was not until ten years later that studies started to answer this question. Naeye (1979) studied approximately 44,500 cases which were followed prospectively from 1959

to 1966, to determine the relationship of pregravid weight status and weight gain to pregancy outcome. Maternal weight gains which minimized fetal and neonatal deaths were defined as 30 lbs for underweight, 20 lbs for normal weight, and 16 lbs for overweight women. Perinatal mortality rates were elevated for the three weight categories when women gained more or less than these optimum values. However, pregnancy outcomes of the overweight women were less affected by variations in weight gain than the women of other weight groups. This study did not use infant birthweight as an outcome measure, but it clearly demonstrated the importance of maternal prepregnancy weight status, an issue which attracted much more attention in the years to follow.

Looking specifically at birthweight as the dependent variable, some studies found a linear relationship with weight gain for women of all weight categories, while others found this relationship did not hold for obese women. In a comparison of 300 pregnancies before 1970 with 300 pregnancies after 1972, Gormican et al. (1980) found that the latter group gained more weight (69% gained >20 lbs) and were delivered of infants with significantly higher mean birthweights. When the two groups were combined and stratified for prepregnancy weight status into underweight (<90% of the standard according to the Metropolitan Life Insurance Company standards (MLI 1959) of weight for height status), normal weight (90 to 120%), and overweight (>120%), the authors found a linear relationship between weight gain and birthweight among all three groups. Unfortunately the analyses did not control for gestational length, maternal age, smoking, race, socioeconomic status or infant sex.

Other studies demonstrated that the association between weight gain and birthweight diminished as pregravid weight increased (Rosso 1985, Abrams and Laros 1986, Brown et al. 1986, Mitchell and Lerner 1989). Abrams and Laros (1986) examined 2946 pregnant women and stratified the sample into four categories according to MLI standards of prepregnancy weight-for-height.

The Institiute of Medicine (IOM 1990) developed and recommended stratification of maternal weight according to prepregnancy body mass index; these strata correspond to the MLI standards of prepregnancy weight-for-height as listed below.

Classification of maternal prepregnancy weight-for-height status

Weight for height	BMI	1959 MLI, %
Underweight	< 19.8	< 91
Normal weight	19.8 to 26.0	91 to 120
Overweight	> 26 to 29.0	121 to 135
Obese	> 29.0	> 135

The results of the multiple regression analysis, which adjusted for gestational length, maternal age, race, parity, weight gain, socioeconomic status, and smoking, indicated that both pregravid body mass and weight gain significantly influenced birthweight for the underweight , ideal weight and moderately overweight women; but for obese women weight gain did not influence infant birthweight. The women in the study of Abrams and Laros (1986) were mainly middle class, but similar results were later found in a lower class sample of women (Frentzen et al. 1988).

The incidence of macrosomia increases as maternal weight increases. When macrosomia was defined as a birthweight greater than 4500 g, it was reported that women with pregravid weights greater than 90 kg (Spellacy et al. 1985) or greater than 115% of IBW (Mondanlou et al. 1980) had significantly more macrosomic infants. When defined as a birthweight of more than 4000 g, macrosomia occurred 1.5 to 2 times more in women with pregravid weights above 70 kg, or weight gains above 20 kg, and heights above 169 cm ($p<.001$) (Boyd et al. 1983). In very obese women (>150%) the incidence of infants weighing more than 4000 g was 4 times higher than in the non-obese controls ($p<.001$) (Edwards et al, 1978).

It is well known that obese women have heavier babies, but it is not well understood how weight gain in obese women does not have a significant impact on birthweight. As nutritional predictors of infant birthweight, prepregnancy weight and pregnancy weight gain act independently, and it seems that the effect of obesity overrides that of weight gain (Kliegman and Gross 1985). The physiological interactions of these nutritional predictors require investigation to provide insight into these relationships. In the meantime, it appears that efforts to minimize weight gain in very overweight women during normal pregnancy may not reduce the risk of having a high birthweight baby, but it is likely better for the mother given the associated risks of obesity in both the gravid and

non-gravid state.

D.2.2 Pattern of weight gain

The classic pattern of gestational weight gain proposed by Hytten and Leitch (1970) does not consider variation in pregravid weight. In an attempt to incorporate this variable into recommendations of weight gain throughout pregnancy. Rosso (1985) developed a chart for patterns of weight gain after 12 weeks gestation, for women over 20 years of age and between 70 and 130% of their ideal body weight (IBW). It indicates that women should gain 20% of their IBW, unless they are greater than 100% and less than 130% of IBW; women in this weight category are recommended to gain 7 kg at term. These patterns were based on the findings that weight gain during pregnancy significantly influences birthweight of infants whose mothers weigh 110% or less of their IBW (Rosso 1985). More recently, Lawton et al (1988) studied the effect of weight gain pattern on low birthweight and found the rate of weight gain between 28 to 32 weeks of gestation to have particular significance in predicting low birthweight in normal pregnancy. Weight gain patterns for twin pregnancy, which fall off after 30 weeks to a total gain of less than 40 lb, were found to predict less-than-optimum outcomes, after controlling for most known confounders except pregravid weight (Pederson et al. 1989). The influence of the pattern of weight gain on birthweight remains to be fully understood, particularly in obese women who may be advised to limit their rate of weight gain.

D.2.3 Energy intake

Research assessing the impact of energy intake on weight gain and/or birth weight has focused on two areas: supplementation trials and dietary restriction, because of the difficulties in assessing dietary intakes in free-living populations. Fetal growth and development require additional energy and as such energy intake is closely associated with gestational weight gain; it would seem logical that as the energy intake increases during pregnancy, so would substrates available to the fetus, which would result in a larger neonate. However these relationships are not so straight forward, as the effects of diet on birthweight are not independent of the effects of weight gain and are similarly subject to the

numerous confounders.

From the meta-analysis of many studies, including supplemental trials in Bogata and Guatemala, additional energy intakes caused a significant positive effect on birthweight, provided the mother was not well-nourished prior to pregnancy; the supplementation trials in New York City and Taiwan did not show an effect of supplementation in adequately-nourished mothers (Kramer 1987). The importance of timing of supplementation was not conclusive. The sample-size-weighted effect of a supplement of 100 calories per day throughout pregnancy was an increase in birthweight of 100 grams for infants born to mothers who were at least moderately malnourished (Kramer 1987). This effect was reduced by two-thirds in women who were not malnourished. Nutritional status was usually based on pregravid weight, but was not consistently reported.

Energy deprivation as reported in the Dutch Famine study (Stein and Susser 1975a,b) had the most impact on birthweight when restriction occured in the third trimester of pregnancy. In terms of the physiology of pregnancy, maternal stores of fat have already been accrued, but this is the period of maximal fetal growth. Such a restriction would put the mother and fetus in competition for her nutrient stores, which would likely be a problem if the mother was lean prior to pregnancy. However if the mother was obese, an ample supply of energy stores should protect the fetus from sub-optimal growth in the event of dietary restriction. Unfortunately few studies address the issue of energy restriction during pregnancy, but those studies (Abrams and Laros 1986, Frentzen et al. 1988) which demonstrated that limited weight gain among obese women did not have a significant impact on birthweight give reason to speculate further about the relationship between body mass and energy restriction during pregnancy.

D.3 Predictors of Birthweight in Gestational Diabetes

It is not clear that the predictors of birthweight in gestational diabetes are the same as in normal pregnancy, although it is a widely held belief. To date, the primary variables investigated for their impact on neonatal outcome in gestational diabetes have been glycemic control and maternal obesity (Jacobson and Cousins 1989, Maresh et al. 1989, Langer et

al. 1989), but the independence of these and other predictors on infant birthweight, has not been comprehensively measured in this high-risk population. Of the limited number of studies in this area, only a few have employed multivariate analysis techniques (Sepe et al 1985, Forsbach et al. 1988), and only one study with a small sample has included nutritional parameters (Algert et al. 1985).

D.3.1 Glycemic control: Diet versus Insulin Therapy

Several studies have attempted to answer the question: does prophylactic insulin reduce the incidence of macrosomia and the related morbidity more significantly than dietary management alone? However it is not clear from the reports which advocate the use of prophylactic insulin, that all GDM would actually benefit from this therapy. Coustan and Imarah (1984) studied three groups of GDM women: one group received insulin and diet therapy, the second group received only diet therapy and the third received no treatment at all. The authors reported that the insulin group had 7% macrosomic infants, significantly less than the similar rates of about 18% in the other two groups. Birth trauma was also lower in the insulin group, 4.8% compared to 13% and 20% in the diet and no treatment groups respectively. However there were problems with the studies design because the groups were not randomly assigned. The method of assigning the women to each group involved offering insulin to the GDM women, and if they declined they were put in the diet group; it is not clear how the women in the third group were recruited. This method could result in selection bias among women who were more motivated or more concerned about their condition, and therefore decided to obtain a higher level of treatment. It is curious that the women on insulin therapy had higher plasma glucose values. There were significant inter-group differences which could affect birthweight: the insulin group was diagnosed earlier and had more glucose intolerance; the diet group gained more weight; and the group which received neither treatment had a significantly higher proportion of whites (white race increases birthweight {Kramer 1987}). It was not reported how dietary compliance was monitored. Although they conclude that prophlactic insulin prevents macrosomia and related birth trauma, this study is clearly flawed and biased.

More recently Thompson and coworkers (1990) conducted a randomized trial of 68

GDM to determine if insulin and diet reduce maternal and neonatal morbidity when compared with diet therapy alone. They used the same diet and insulin regimens as Coustan and Imarah (1984) and treated the women with GDM for 11 weeks prior to delivery. Mean fasting blood glucose was not different between the diet (4.3 mmol/L) and the insulin group (4.4 mmol/L). The mean birthweight of the diet group (3584 g) was significantly higher than the insulin treated group (3170 g). The incidence of macrosomia, defined as a birthweight greater than 4000 g, was also elevated in the diet group (26.5% versus 5.9%), however there was no significant difference in the incidence of perinatal morbidity. The authors concluded that insulin was not detrimental and that the decreased birthweight benefits the neonate, however these results more clearly indicated that diet treatment alone resulted in similar glycemic control as the insulin group and heavier babies without increased morbidity.

Leikin et al. (1987) conducted a case control study of 181 GDM and 1850 controls to determine factors associated with increased risk of macrosomic infants. The women with GDM were treated with diet if fasting plasma glucose (FPG) was <5.0 mmol/L and with insulin if FPG ≥ 5.0 mmol/L. They found the rates of macrosomia in the diet-treated group (5.6%) and the controls (6.4%) were similar and significantly lower than those of women on insulin (16.2%); and they found the non-obese GDM women treated with insulin did not have more macrosomic infants than the non-diabetics and diet treated group. Logistic regression indicated that obese women on insulin were at greater risk of having macrosomic infants. Maternal and neonatal morbidity were not different from the controls. This study refuted the findings that insulin reduces the incidence of macrosomia and indicated that diet management alone is appropriate for GDM with fasting euglycemia, however the question that remains is if the non-obese women on insulin could also be managed with diet alone.

D.3.2 Energy Restricted Diets

Many studies report they prescribed diets for GDM without any indication of what was actually consumed and how compliance was measured. Algert et al. (1985) included this dietary information and attempted to link some of the potential nutritional predictors to

infant birthweight. This study compared the effects of moderate caloric restriction in 22 obese (BMI≥27) GDM with less restricted diets in 31 lean GDM and 10 non diabetic non obese controls, by evaluating actual energy intakes, total gestational weight gain, glycemic control, and birthweight. The diabetic diets prescribed were comprised of 1700-1800 kcal/d for the obese and 2000-3000 kcal/d for the lean GDM; the non-diabetic subjects were advised to consume their regular diet for pregnancy, and to eat to appetite. Food records were collected and compliance was assessed such that the dietary intakes were closely monitored for the 10 to 15 weeks of treatment prior to delivery, and were 1750±188 kcal/d for the obese GDM, 1822±224 kcal/d for the lean GDM and 2282±524 kcal for the controls. Ketonuria was not found at weekly measures. Total gestational weight gain was significantly lower in the obese GDM women than in the other two groups, mean birthweight was higher among the obese, and glycemic control as measured by hemoglobin A1C was not different among the groups. Unfortunately linear regression failed to show any effects of prepregnancy body mass and weight gain on birthweight, most likely due to the small sample size. However this study suggested that a modest energy restriction for obese women with GDM may not give rise to ketonuria, or cause a marked reduction in birthweight.

D.3.3 Maternal Size

Hollingsworth (1986) suggested that the most distinguishing feature of gestational diabetes (GDM) is maternal size, as it acts as a modulator for insulin and glucose responses in the fasting and fed state. Both poorly controlled GDM and obesity can result in an abundant supply of fuel for the fetus, which is believed to be a major factor in macrosomia (Kliegman and Gross 1985). However when GDM is well-controlled as is often the case in antenatal centres with intensive management protocols, macrosomia is attributed to maternal obesity. Recent studies have attempted to distinguish between the influence of body habitus and severity of diabetes on birthweight.

Langer and coworkers (1989) compared 334 GDM mothers to controls matched on obesity, race and parity. Among the infants born to the GDM mother, there was a strong association between low levels of plasma glucose and small-for-gestational-age (SGA)

infants (birthweight < 2500g). Conversely, high levels of mean plasma glucose were associated with LGA infants Stepwise regression analysis of the GDM women indicated that hypertension and previously having a LGA infant were not significant predictors of birthweight; and that blood glucose, weight gain and gestational age were predictors and accounted for 11% of the variation in birthweight. This analysis did not control for smoking, maternal height and infant gender.

Recent evidence suggested maternal weight at delivery was the only significant predictor of infant birthweight in GDM (Jacobson and Cousins 1989, Maresh et al. 1989). Jacobson and Cousins (1989) studied the maternal and perinatal outcome in a prospective population-based study of patients with GDM and used stepped multiple regression to determine the predictors of birthweight. Numerous variables were entered into the model: race, socioeconomic status, maternal age, gravidity, parity, height, prepregnancy BMI, prepregnancy weight, total weight gain, weight at delivery, length of treatment, smoking status, OGTT values, treatment, insulin dosage, and mean fasting and post-prandial blood glucose values. This model contains several correlated variables which should not be in the same regression because they influence each other and mask the true effect each may have independently, for example prepregnancy BMI and prepregnancy weight are highly correlated since they are both measures of fatness and the latter is the numerator of the former. In addition, total weight gain is represented in weight at delivery, which means these variables are correlated. On the other hand BMI and height can go in the same model because they are not correlated, one represents fatness and the other stature. None-the-less this regression found that weight at delivery was the only predictor of birthweight and explained 11% of the variance in birthweight. Although the major predictors of birthweight were controlled for, maternal weight at delivery may have masked any effects due to pregravid weight status and weight gain during pregnancy , since direct determinants can wipe out the effect of indirect determinants. Jacobson and Cousins (1989) proposed that the accelerated growth *in utero* common to infants of GDM may be due to the metabolic disturbances of obesity rather than those related to well-controlled GDM.

These findings were supported by Maresh et al (1989) who reported that increased birthweights were strongly associated with maternal obesity (based on BMI just prior to

delivery), while only possibly associated with diabetic control. This study matched GDM mothers to non-diabetic mothers for age, parity and ethnic group, and found that obesity was a predictor of LGA independently of the severity of diabetes, but known predictors of infant birthweight such as maternal height, weight gain during pregnancy and smoking were not controlled. They also found that neonatal morbidity was associated with severity of diabetes, and not to age or obesity.

Maternal size clearly exerts an influence on birthweight in GDM pregnancy; the problem with this variable is that maternal obesity was based on weight at delivery and therefore may reflect an obese prepregnancy weight and/or an excessive gestational weight gain. Both of these variables independently increase birthweight in normal pregnancy and should be analyzed more carefully in GDM pregnancy. The GDM literature to date also lacks examination of how predictors change among non-obese and obese women.

D.3.4 Weight Gain as a Predictor of Birthweight in GDM

Although gestational weight gain has been accepted as an important predictor of birthweight in normal pregnancy (Kramer 1987, Abrams and Laros 1986), it has lacked attention in studies of GDM. The limited number of studies that have included weight gain as a predictor of birthweight contradict one another. One study found weight gain was a predictor of infant birthweight (Langer et al. 1989), while another study found it was not a predictor (Jacobson and Cousins 1989), and another did not consider weight gain as an independent variable at all (Maresh et al. 1989). Most studies have not found a significant difference between weight gained by women with GDM and that of controls (Buchanan et al 1990, Maresh et al 1989, Jacobson et al 1989, Langer 1989), although one study did report that obese women with GDM gained significantly less than lean GDM and controls (Algert et al. 1985).

E. Hypotheses

Maternal nutritional status of the gestational diabetic, as reflected by prepregnancy weight and gestational weight gain and influenced by dietary intake, has a significant impact on infant birthweight when the confounding effects of maternal age, height, smoking, parity, gestational age, infant gender and plasma glucose are controlled.

The study objectives are to:

1) Characterize dietary intake and gestational weight gain of women treated for gestational diabetes;
2) Determine how dietary treatment alone affects weight gain and glycemia during treatment of GDM, and how it affects infant birthweight;
3) Determine the independent predictors of infant birthweight in GDM;
4) Evaluate the modification of predictors of birthweight by prepregnancy body mass;
5) Examine the predictors of macrosomia in infants born to mothers with GDM.

F. Significance of the Study

The proposed study, with its large database and sample size of women with GDM and their infants, has the potential of answering several questions not yet investigated.

This study has the potential to establish whether the predictors of birthweight in infants born to gestational diabetic mothers are similar to those for offspring of non-diabetic mothers. While Kramer (1987) has identified 14 predictors of birthweight in normal pregnancy, only glycemia and maternal obesity have been linked to GDM.

Maternal obesity, which has been defined as weight at diagnosis or delivery, could represent an obese prepregnant weight or excessive gestational weight gain or both; the influence of these independent components can be measured for the first time in the diabetic population. The modification of predictors of birthweight by prepregnancy body mass index among GDM can be evaluated for the first time with proper control of confounding variables. Abrams and Laros (1986) indicated that weight gain during normal pregnancy does not significantly influence birth weight in the obese non-diabetic women. If this

observation holds for obese gestational diabetic women, then attempts at modifying the rate of weight gain during pregnancy to decrease macrosomia in this group would be futile

The proposed study can verify whether glycemic control by means of diet and/or insulin therapy modulates birthweight. Dietary management alone can be described in terms of reducing plasma glucose, minimizing weight gain and thereby influencing fetal growth.

For the first time, energy and macronutrient intake during treatment of GDM can be evaluated as to their impact on gestational weight gain, glycemic control and birthweight The current belief is that energy restrictions could lead to a reduction in LGA, but it has not been demonstrated in this population.

Part II

Methods

A. Overview

B. Subjects

B.1 RVH Screening and Diagnosis of GDM
B.2 RVH Antenatal Diabetic Clinic Treatment Protocol
B.3 Subject Selection

C. Data Collection and Management

C.1 Diabetic Data for Eligibility
C.2 Diabetic Data for all Included Subjects
C.3 McGill Obstetrical and Neonatal Data System (MOND)

D. Analysis

D.1 Statistical Methods
D.2 Sample Size Calculation

E. Facilities

A. Overview

This study involved a large cohort of women with gestational diabetes mellitus (GDM) and their infants, and was conducted in the Spring/Summer of 1991. Maternal and neonatal data were collected from a chart review of the 1003 patients followed at the Royal Victoria Hospital (RVH) Antenatal Diabetic Clinic between 1978 and 1989, inclusive.

Management of GDM at the RVH has been intensive, consistent and comprehensive since it's origin in 1978. Close multi-disciplinary antenatal monitoring of patients on a weekly basis, as well as self-monitoring on a daily basis, contribute to the high quality of data available for abstraction and analysis.

Data were obtained from two sources: the RVH Antenatal Diabetic Clinic (ADC) chart: the source of diabetic monitoring information from diagnosis to delivery; and the maternal and neonatal medical chart data already coded on the McGill Obstetrical and Neonatal Data System (MOND) (1987).

Descriptive analyses were used to study the relationships between independent variables, and were followed by a series of multiple regression analyses using independent variables which were clinically relevant to the dependent variable, infant birthweight. The objective of the study was to thoroughly describe and evaluate the nutritional predictors of infant birthweight in gestational diabetes.

B. Subjects

B.1 Royal Victoria Hospital Screening and Diagnosis of GDM

Patients are referred to the ADC by their attending physician once gestational diabetes or impaired glucose tolerance is detected. Screening and diagnostic procedures used at this institution are in accordance with the criteria of the National Diabetes Data Group (NDDG), outlined in section B.3 of the Literature Review. However, some obstetricians order a screening test only when a patient presents with risk factors or symptoms of GDM, rather than apply the universal screening recommendations of the NDDG.

A diagnosis of impaired glucose tolerance (IGT) is made if one OGTT value is met or exceeded (OGTT values in mmol/L: fasting 5.8, 1 hr 10.6, 2 hr 9.2, 3 hr 8.1).

Gestational diabetes is diagnosed if 2 or more of the OGTT criteria are met or exceeded. White's classification (1965) of diabetes in pregnancy (see Appendix I) is used for diagnostic purposes to indicate the severity of the diabetes. The subclassification of diagnosis is based on the mode of treatment required: class A1 diabetics receive diet therapy alone; class A2 diabetics receive diet and insulin therapy. Patients with IGT are treated identically to those with class A1 diabetes. During the treatment period the severity of diabetes may progress such that the diagnosis is changed from impaired glucose tolerance (IGT) or class A1 diabetes to class A2 diabetes.

B.2 RVH Antenatal Diabetic Clinic Treatment Protocol

The therapeutic approach is comprised of multi-disciplinary assessment and regular follow-up by the team of clinic nurse, dietitian, endocrinologist and perinatalogist. At the initial visit the team members gather information on the patients' medical, obstetrical, nutritional and sociodemographic history, which permits them to formulate an assessment and plan. Generally the plan involves a weekly visit to the clinic for evaluation of diabetic control and daily self-monitoring of fetal health and certain components of diabetic care. The patient's weekly visit is comprised of the following routine:

Arrive at the clinic at 7h30;

Have fasting blood taken for glucose measurement and any other tests which may have been ordered, (glycosylated hemoglobin is measured at initial visit and approximately once a month therafter);

Provide fresh urine sample for glucose, ketone, protein and leukocyte testing;

Take weight on clinic scale;

Eat breakfast provided by the Dietetics department based on each patient's diabetic diet pattern;

1 hour post-prandial have another blood sample taken;

Nurse takes blood pressure, assesses for peripheral edema, conducts non-stress test for fetal activity and reactivity;

Dietitian reviews food intake records, urine (and blood when applicable) tests from past week, and weight: adjustments to and reinforcements of diet are made as

needed;

Eat lunch;

Endocrinologist reviews urine tests, blood tests, dietary compliance and insulin if applicable, assesses the need for initiation of insulin and makes changes to insulin dosage and sliding scale if necessary;

Perinatologist assesses maternal and fetal health with physical exam; reviews results of non-stress test results, blood pressure, fetal movement charts, and ultrasound if applicable; makes orders when necessary for bed rest,admission, delivery, and medication;

Finish by 15h30 to 17h30, depending on the number of patients being seen.

Patients retain a sense of involvement and responsibility in their prenatal care by monitoring their own diabetic management and control each day in between clinic visits. This is accomplished by the following activities:

Record of daily food intake, food is weighed and measured according to the diabetic diet prescription;

Record of fetal movements on a chart to ensure a minimum of 10 movements each day, as a measure of fetal well being;

Measure of urinary acetone and glucose, taken 4 times per day (before each meal and before the bedtime snack) and recorded;

Blood glucose monitoring if taking insulin, 4 to 7 times per day (before and after meal);

Insulin administration and adjustment as per a prescribed dose and sliding scale, when dietary management fails to render euglycemia.

All of the variables related to diabetic management prior to delivery originate from the ADC chart (refer to Appendix V for variable definitions). A more detailed description of the origin of the dietary data will be given below.

Dietary Objectives

The objectives of diet therapy at the RVH diabetic clinic are to provide adequate nutrition in order to: (1) permit normal fetal growth; (2) maintain maternal nutrition; (3) optimize blood glucose levels; and (4) avoid ketonuria.

Dietary Prescription

Energy content of the prescribed diets is based on approximately 35 kcal/kg of ideal body weight and generally range from 1800 to 2200 kilocalories (7760 to 9440 kilojoules) initially, with increments or decrements when necessary, as described below. Carbohydrate is limited to 40% of energy or less and is divided throughout the day. Patients are taught a very specific and individualized diabetic diet using a booklet adapted from the Canadian Diabetes Association Good Health Eating Guide, formerly the Diabetic Exchange System. The meal plan consists of 3 meals and 3 to 5 snacks spread over the day according to each patient's routine. It is not uncommon for the GDM patients to be overweight prior to pregnancy or to have gained weight excessively prior to diagnosis, hence dietary restriction used to obtain the four objectives outlined above, often results in a marked reduction in weight gain pattern at least initially. However, post-diagnostic changes in weight gain pattern are not the focus of treatment.

The dietary prescription may be changed during treatment, with increments and decrements of specific foods or "choices" according to the diabetic diet; for example the addition of a "protein choice" will increase the diet by 73 kilocalories, 7 grams of protein and 5 grams of fat. A diet will be increased if ketonuria is present on a regular basis in significant amounts, for example 2+ to 3+ ketonuria on three consecutive mornings. Ketones may be present if a woman has not consumed part or all of a meal or snack; in these situations the importance of dietary compliance is stressed. Ketonuria can also occur when the prescribed energy level or dietary composition is inadequate, in which case the diet is increased in total fat and protein. Carbohydrate is not increased as often as other macronutrients due to it's glycemic effect. If glucosuria or hyperglycemia occurred when the diet was followed, carbohydrate may be reduced at the related meal or snack. However, more often these are indications of poor compliance or the need for insulin.

Energy intake may also be increased if a patient is consistently hungry, however an initial attempt may be made to rearrange dietary pattern. A diet will be decreased if excessive weight gain (>0.35 kg/week) cannot be attributed to edema or dietary intake above the prescribed regimen, or if a patient cannot consume the entire diet.

Diet methodology

The prescribed diet is instructed to each patient by the dietitian, during their initial visit. A very specific pattern, which indicates the number of choices from each food group to be consumed at each meal and snack, is provided along with a booklet which describes the type and quantity of foods included in each food group. The role of the diet in controlling glycemia and the implications of control of GDM for the fetus are explained to each woman. Patients are given the opportunity to ask questions during the instruction of the diet. Patients are told to measure or weigh all the food and beverages they consume according to the prescribed diet, as well as any additional food they may have taken. A record of their daily food intake is requested by the dietitian for each week that the patient attends the clinic, and the women are advised to include a description of the food and method of preparation. Meals eaten away from home should be recorded as accurately as possible. The food record is reviewed throughout the period from diagnosis to parturition by the dietitian and the endocrinologist. This method of daily weighed food records has been described by Gibson (1990), as being the most precise method for estimating dietary intake and essential to derive good quality data for statistical analysis. Illiteracy and language barriers can pose problems with the use of this method. Dietary instruction is simplified for illiterate patients and includes the use of food models; if a patient cannot speak english or french a translator is often used (a family member is preferable) to explain the diet and to interpret food records.

Patient compliance to the prescribed dietary regimen is difficult to establish with complete confidence, however there are indicators during treatment that a patient probably complied with the diet, as well there are factors which contribute to dietary adherence among these women. Daily self-monitoring of urine for glucose and ketones can provide clues to compliance; if additional carbohydrate is taken it may manifest as glucosuria,

conversely if all the diet is not eaten ketonuria could occur; granted both glucouria and ketonuria can occur for other reasons as described earlier. Self-monitoring and recording of blood glucose can also indicate dietary excesses or inadequacies. It was the personal experience of the author that patients often recorded their dietary indiscretions directly on the monitoring sheet for urine and blood glucose if not on their food record, to explain the appearance of abnormal values. Factors which contribute to patient compliance include the implicit motivation of the pregnant woman to do what is best for her growing baby; the additional incentive to follow instructions for the management of the high-risk condition which could affect pregnancy outcome, and the presence of other women with GDM at the clinic provides peer support to follow the diet and record dietary intake.

Patient compliance, comprehension and adequacy are evaluated by the dietitian each week. The dietitian uses the patient's food intake record to verify the accuracy and suitability of the diet ingested with the patient's actual prescribed pattern. If the diet was misunderstood, poorly followed or ignored, the diet and it's importance would be re-explained. Discrepancies are recorded, such that actual intake of calories, carbohydrate, protein and fat can be compared with the diet prescription. The dietary approach enforced at this clinic has been consistent since the clinic's origin in 1978; dietary adherence is also emphasized by the other members of the team as a crucial element of GDM management.

Insulin therapy is currently initiated if diet therapy does not maintain fasting plasma glucose values less than 5.0 mmol/L (90 mg/dl) or the 1 hour post-prandial values less than 6.7 mmol/L (120mg/dl). Prior to 1985, insulin therapy was initiated only when FPG exceeded 5.3 mmol/L or the 1 hour PC exceeded 7.2 mmol/L. Human insulin is prescribed, and usually begins with small amounts (2-4 units) before breakfast, although it is not uncommon for a class A2 diabetic to have an insulin regimen with 2 to 4 injections per day. Patients are taught how to inject insulin and test capillary blood samples using a glucometer provided by the clinic. The endocrinologist prescribes a sliding scale for insulin dosage, such that patients can adjust their own insulin dosage according to their daily home-blood-glucose-monitoring (HBGM) results. Each week the endocrinologist reassesses the insulin therapy regimen.

Other self-monitoring procedures involve urine testing 4 times daily, before each meal and before bed. Chemical dipsticks are used for determination of glucosuria and ketonuria. A record of urine testing is kept by each patient and reviewed by the clinic team each week.

The regimen at the GDM clinic is demanding and requires that patients attend the clinic once each week from 7h30 to about 15h30, from the time they are diagnosed until parturition. Compliance with the prescribed protocol among the gestational diabetics is exceptional; these women have always been found to be highly motivated to attend the clinic each week and bring their records of self-monitoring. They are willing to take heed of the numerous recommendations in order to optimize their diabetic control and therefore optimize their pregnancy outcome.

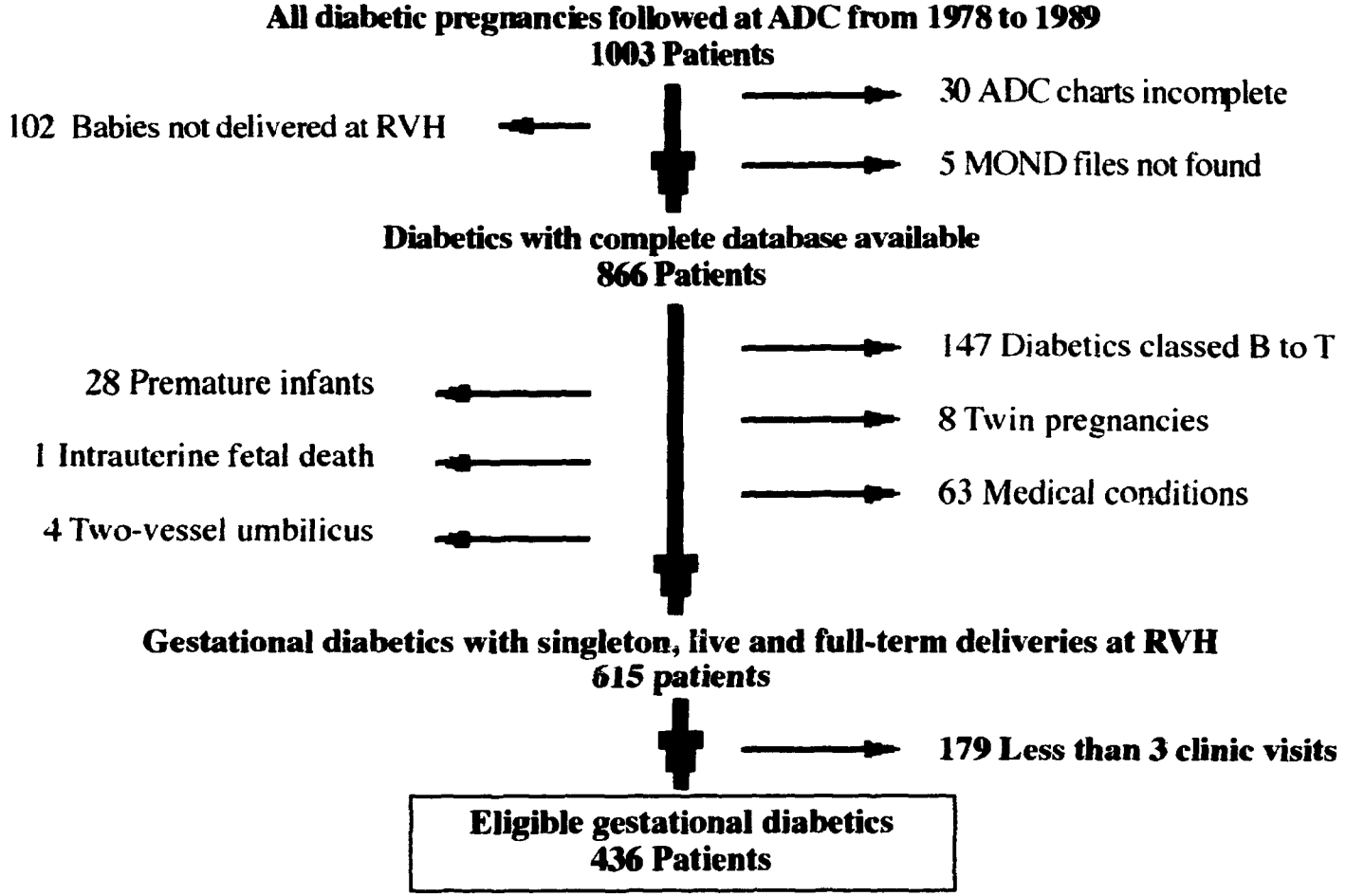
B.3 Subject Selection

All Diabetic Clinic charts were reviewed to determine each patients' eligibility status for the study. Subjects were included if they had been diagnosed with IGT or Class A1 or A2 GDM; they presented to the diabetic clinic prior to 36 weeks gestation or had more than two visits to the ADC ; and their baby was delivered at the RVH. The cut-off point of more than two visits to the clinic was arbitrary and was established in attempt to eliminate patients with a minimal amount of treatment prior to delivery, since the effect of certain treatment variables was being evaluated. Exclusion criteria include patients who had pre-gestational diabetes, conditions which affects fetal growth (listed in section C.1), twin pregnancies, or incomplete records from either of the data sources. Figure 3 illustrates the entire cohort of diabetics as the exclusion criteria were applied.

C. Data Collection and Management

Data collection was divided into three stages which will be described below. The procedure facilitated exclusion of ineligible patients at the earliest possible point in the process, and thus minimized unnecessary data collection. A triplicate Diabetic Coding Form (see Appendix II) was developed for the recording of all diabetic information, and

Figure 3. Eligibility flow chart



was used for the first two stages of data collection.

C.1 Diabetic Data for Eligibility

Antenatal Diabetic Clinic (ADC) charts were examined starting with 1978 and proceeding alphabetically through each year to 1989, inclusive. Part I of the Diabetic Coding form was completed by extracting a number of variables from the chart to determine the eligibility status, as outlined in section B.3 Subject Selection. The procedure by which each variable was obtained will be described below.

General Information

The following variables were abstracted from the ADC chart for part I of the data collection: mother's name (maiden, if available; married and first name); RVH case number; name of referring doctor; date and results of the glucose screen; date and results of the oral glucose tolerance test (OGTT); diabetic diagnosis; and complications or risk factors. Each of these variables could be found on a weekly summary at the front of the chart,as well as on consultations and lab results within the chart; this duplication provided a means of verifying the accuracy of the data.

The delivery date, sex and birth weight of the infant was also recorded on Part I of the coding sheet. These variables, along with the names and RVH case numbers permitted the linking of each person in the cohort with their respective data in the McGill Obstetrical and Neonatal Database (MOND).

Diagnostic Information

Diagnosis of gestational or pregestational diabetes was indicated on the flowchart, according to White's Classification of Diabetes in pregnancy (see Appendix I). For patients with impaired glucose tolerance (IGT) or gestational diabetes (GDM) the OGTT results were compared to the criteria of the National Diabetes Data Group (NDDG) to ensure an accurate diagnosis. If any uncertainty arose as to appropriate diagnosis of White's classification, the clinic's endocrinologist was consulted. A change of diagnosis was normally used to indicate the initiation of insulin in a patient with IGT or class A1 GDM,

after at least 3 visits to the clinic. If insulin was started before the fourth visit, a diagnosis of class A2 would be assigned; that would not be considered a change in diagnosis for the purposes of this study.

Eligibilty Status Information

The criteria for exclusion from the study are listed in Table 1. The endocrinologist's consult provided the most thorough and reliable information on the patients' diabetic diagnosis and past medical history. Patients with impaired glucose tolerance and gestational diabetes were included in the study. All those with other classes of diabetes, that is who developed the disease prior to pregnancy, were excluded. Women who were diagnosed postpartum with diabetes and returned to the ADC for a subsequent pregnancy were not included in the study.

Some women were referred to the ADC for management of GDM from other centres, and as long as they met the other criteria and they were delivered of their infants at the RVH, they were included in the study. If a patient was referred from the Lakeshore General Hospital for example, then followed at the ADC until close to the estimated date of confinement, but was assumed to have not delivered at the RVH as the infant was not found in MOND, she was excluded from the study.

The effect of treatment is an important aspect in this study, thus a minimum length of treatment period had to be established. The cut-off point of no less than 3 visits over a minimum of 3 weeks was arbitrary. If a patient started treatment at the clinic, then discontinued follow-up for more than two weeks prior to delivery they were excluded as well. However if a women with GDM was admitted to the hospital for a short period during treatment then returned to the clinic to be followed until delivery, she would be included since in hospital diabetic management would have continued, and her weight prior to delivery would be available. If she remained in hospital until delivery she would have to be excluded due to the lack of data. The women excluded for less than 3 clinic visits generally represent women who were referred to the clinic or diagnosed late in their pregnancy, rather than women who did not comply with the clinic protocol by attending each week, although there were a few women who fell into the latter category.

Table 1. Exclusion Criteria

1. Antenatal diabetic clinic chart incomplete, for example no pregravid weight
2. MOND file on mother and infant not found or missing information (eg. pregravid weight)
3. Infant not delivered at the Royal Victoria Hospital
4. White's class of diabetes B to T, that is pregestational diabetes (see Appendix 1)
5. Twin pregnancy
6. Presence of condition or medication which could affect fetal growth
7. Premature infant (<37 weeks gestation)
8. Intrauterine fetal death (IUFD)
9. Neonate with a 2-vessel umbilical cord discovered at birth (normally 3 vessels)
10. Less than 3 visits to the diabetic clinic prior to delivery

Complications or risk factors identified in the chart often provided important clues to the patients eligibility status. For example, if it was indicated that the patient was having twins or was taking medication for chronic hypertension, the patient would be excluded. Below is a list of the conditions which were discovered among the cohort and were grounds for exclusion for their potential influence on fetal growth and consequently infant birthweight, the dependent variable under investigation.

Chronic hypertension	Active asthma
Pyelonephritis	Rh isoimmunization
Pre-eclampsia	Lupus
Nephrotic syndrome	Gluten enteropathy
Ulcerative colitis	Cystic fibrosis

Thrombocytopenia (treated with high dosage of prednisone)

The following list indicates conditions which were not considered for exclusion, and therefore patients with them remained in the study.

Anti kell antigen	Hepatitis B
IgA nephropathy	Von Willebrand II
Depression	Raynaud phenomena
Mild Asthma	Treated hyperthyroidism
Treated hypothyroidism	Hyperlipidemia
Bell's palsy	Prolactinoma

Infant birthweight after treatment for gestational diabetes was the primary outcome variable studied, and therefore only term (≥37 weeks) deliveries of healthy, live infants were included. Maternal-neonatal cases were excluded if they involved an intra-uterine fetal death (1), an infant with a 2 vessel umbilical cord (3) or premature infants (27).

Data Management

At the end of every day of data abstraction, all patients reviewed, whether included or excluded, were consecutively assigned a study number. The top sheet of the triplicate form was removed and delivered to the MOND Research Assistant Frances McLean. A master list was generated by entering the following data into a database program: study number, mother's name and case number, baby's case number if known, diagnosis, change in

diagnosis, eligibility status and comment if needed. This program permitted a count of cases in each category of eligiblity and the generation of lists of included and excluded patients for easy verification of information collected. Back-up files were made and maintained in a different location for security purposes.

C.2 Diabetic Data for Included Subjects

Part II of the antenatal diabetic coding form (see Appendix II) was completed for the included subjects. This involved collecting data from each clinic visit for current weight, blood glucose (fasting and 1 hour post-prandial), the average daily intake of energy, carbohydrate and protein over the previous week based on diet calculation of 7 day food record, and a summation of urinary ketones recorded over the previous week. Insulin dosage recorded represented units of insulin taken the day before the clinic visit. Glycosylated hemoglobin was recorded as often as it was available, which was generally every 4 weeks.

Accuracy of the dietary information at each visit was also recorded as being either good, fair or poor. This variable indicates if the chart provided enough detail on the dietary evaluation at a particular visit to estimate the daily intake of the previous week. For example, if the dietitian had prescribed a 2000 kilocalorie diet (with 194 g carbohydrate, 111 g protein) the previous week, and follow-up notes indicated: "*dietary compliance was excellent*" then accuracy for the above diet would be coded as 'good'. If she wrote, "*fair understanding of starchy choices; took 1/2 extra bread at breakfast and lunch every day, otherwise good compliance*", then intake would be calculated to include 1/2 extra starch twice each day (2068 calories, 209g carbohydrate, 113g protein); and accuracy would be 'good'. However, if the dietitian's notes indicated that the patient took less than the diabetic diet, but did not quantify the discrepancy, an estimate of the reduced intake would be made, and the accuracy would be rated as 'fair'. The accuracy would be 'poor', if the progress notes implied that dietary compliance was poor without any indicator of how the patient's actual intake deviated from the prescribed plan.

Urinary analysis was done using chemical dipsticks which indicate the presence of ketones with a change in color as none, small amount (1+), moderate amount (2+), or large

amount (3+); these values were recorded by the patients 4 times each day, for every day between visits to the clinic. The frequency and seventy of ketonuria was monitored daily by each patient. The endocrinologist evaluated the patient's log of ketonuria according to frequency and severity and charted her assessment, for example her chart entry may indicate "*no ketones*", or "*2+ ketones three times, otherwise none*". This data was coded during data collection as a variable hich summarized the patient's findings per visit using five categories; these categories were established arbitrarily in consultation with the clinic endocrinologist. The categories for the ketonuria variable are: none present (may include 1+ ketonuria one time); present in small amount (1+ two to four times, 2+ one to four times, or 3+ once); present in moderate amount (1+ >four times, 2+ five to eight times, or 3+ two to seven times); and present in large amounts (2+ >eight times, or 3+ >seven times). Combinations of severity of ketonuria were coded according to the discretion of the author.

See the coding sheet and definitions in Appendices II and III, for precise explanations of the variables collected in Part II and Appendix V for variable summarization. Once coded on the data sheets, data were entered into a computer data file by professional keypunch operators; verification by entering data a second time was done.

C.3 McGill Obstetrical and Neonatal Data (MOND) System

The McGill Obstetrical and Neonatal Data system (1987) is a database established in 1978. The MOND Coding Manual provides definitions of each variable selected for this study. Access to the system was facilitated by Dr. R. Usher, head of Neonatology, and Ms. Frances McLean RN BScN, who linked each patient included in the study to their MOND file. Data from MOND included maternal demographic information, as well as details on the delivery and status of mother and neonate. See list of maternal and neonatal variables in Appendix IV.

D. Analysis

D.1 Statistical methods

Data analysis was done with the Statistical Analysis System (SAS), version 6.0. The data from the diabetic clinic charts and from MOND were merged on a SAS file for analysis

Variable Summarization

A brief description of how variables used in analysis were defined and coded can be found in Appendix V. The origin of each variable was either MOND or the ADC charts (see Appendix IV).

Descriptive Analysis

Maternal and infant characteristics were summarized for the whole sample initially. Continuous or interval variables were then selected for a one-way analysis of variance which stratified the sample in 3 separate ways: by body mass index (BMI) categories, by treatment categories and by birthweight ratio categories. Frequencies of discrete variables were determined and compared using the χ^2 test. Correlation analysis was used to assess relationships between ketonuria and weekly weight changes. The paired *t* test was used to compare the mean change in rate of weight gain and the mean change in plasma glucose when treatment was started. Results were considered significant if the p value of the analyses was less than 0.05.

Regression Analysis

Multiple linear regression analysis was used to identify predictors of infant birthweight. Because of the expected interrelationships of a number of the predictor variables, several strategies for controlling confounding variables were explored. For example, a statistical interaction was expected between weight gain pattern and pregravid weight. Rather than attempt to model this interaction, it was considered preferable to analyze pregravid weight strata separately. The reason for this was that many variables would interact with weight

gain, for example length of treatment and severity of GDM. In an attempt to reduce the problem of multicollinearity between predictor variables, correlation analysis was done to determine which variables were highly correlated variables, such that they were not entered in the same regression model. For example, a correlation coefficient greater than an absolute value of 0.3 indicates a very high degree of multicollinearity. The conventional definition of level of significance ($p<0.05$) was used to define predictors of birthweight, however for regression modelling, p values of less than 0.2 was considered statistically important and the independent variable was carefully examined in other models.

Logistic regression involved dichotomizing birthweight ratio at 1.25 to determine the incidence of macrosomia among infants delivered of gestational diabetics. Calculations of the odds ratio and Miettinen's test-based confidence interval employed the following equations:

Odds ratio, $\Psi = e^{c\beta}$, where c is the number of units of the parameter being estimated and ß is the estimate;

Confidence interval, $CI = (\theta)\exp[\pm Z_{1-\alpha/2} / \sqrt{\chi^2}]$, where θ is the parameter estimate.

D.2 Sample Size Calculation

The sample size calculations were done prior to commencing the study. Although there is no clear way of estimating sample size for this study since no data are available on post-diagnostic weight gain differences of gestational diabetics, one approach is to base the sample size calculation on differences in infant birth weight previously observed among obese and non-obese gestational diabetics. Using such data to obtain approximate values that might be appropriate for weight gain groups and assuming a 10 % difference in birthweight percentile between groups, with a type I error of .05 and type II of .10, 192 subjects would be required. In order to have this degree of power in 2 substrata of the data that would be best analyzed separately, approximately 400 complete charts would be required.

To analyze macrosomia as a dichotomous outcome, one can estimate the sample size

required for logistic regression analysis as follows. If 10% of infants are affected and it is desirable to detect an odds ratio of 1.5 with Type I error of .05 and type II of .20, the sample size for a univariate logistic regression analysis would be 457 subjects. (Hsieh 1989).

E. Facilities Available

Given it's retrospective nature, this study involved data collection and analysis, but not data generation. Limited resources were required to execute the study Facilities for chart review and storage during data collection were provided by Dr. B. Nuwayhid, Royal Victoria Hospital, Head of Obstetrics. Access to MOND has been provided by Dr. R. Usher, Head of Neonatology, and Ms. F. McLean RN BScN, Research Assistant for MOND. Statistical analyses were conducted on an IBM personal computer. No additional facilities were required.

Ethical approval for this project was granted by the Obstetrics and Gynecology Ethics Committe of the Royal Victoria Hospital. Chart access approval was granted by the hospital's Director of Professional Services.

Part III

Results

A Maternal Characteristics

A.1 Overview of the study population
A.2 Comparison of body mass index groups
A.3 Comparison of treatment groups
A.4 Ketonuria
A.5 Effect of treatment on plasma glucose

B Infant Characteristics

B.1 Overview of infants anthropometric measurements, morbidity and mortality
B.2 Comparison of body mass index groups
B.3 Comparison of treatment groups
B.4 Comparison of maternal and infant characteristics by birthweight ratio
B.5 Secular trends of maternal and infant characteristics

C Predictors of Infant Birthweight in GDM

C.1 Multiple linear regression
C.2 Regression analysis ofwhole sample
C.3 Stratification by BMI categories
C.4 Subset of women of treated with diet alone
C.5 Predictors of plasma glucose
C 6 Logistic regression to evaluate factors influencing macrosomia

NOTE: All tables and figures pertaining to the results are at the end of this section

Both maternal and infant characteristics presented in section A and B were obtained using univariate and bivariate analyses. These statistical methods provided important information regarding trends and potential confounding variables, however since only one or two variables were being controlled at a time, these methods did not provide a clear picture of the factors affecting birthweight. Since birthweight is influenced by many variables, multivariate analysis was necessary to establish the existence, magnitude and direction of the effects of numerous independent variables on the dependent variable, as presented in section C.

A Maternal Characteristics

A.1 Overview of the population

The sample was comprised of 436 women with gestational diabetes (GDM), after the exclusion criteria were applied (see Figure 3 in Methods section). Table 2 shows numerous maternal characteristics. At the time of diagnosis 61% were 30 years of age or older. Forty percent of the women were nulliparous (never pregnant before index pregnancy); 35% were primiparous (one previous delivery), and 25% were multiparous (2 or more pregnancies). Cigarette smoking during the index pregnancy was reported among 96 (22%) of the subjects. Information on race was available for 79% of the sample and indicated that the majority of women studied were white, although smaller groups of black, oriental and East Indian women were represented. Years of schooling varied; 29% of women had a high school education, 23% attended CEGEP or equivalent outside of Quebec, and 43% had some amount of post-secondary education. Most women (95%) reported little or no alcohol consumption during pregnancy; however 1% indicated they drank one or more drinks per day and 4% did not specify any amount of alcohol consumed. The source of this data was a self-administered questionnaire during admission to hospital and the information could not be corroborated by the diabetic clinic dietary data. One percent of women reported the use of cannabis during pregnancy, although frequency of use was not indicated.

Dividing the population into prepregnancy body mass index (BMI) categories as recommended by the Institute of Medicine (1990), 12% of the gestational diabetics were underweight (BMI<19.8), 56% were normal weight (BMI 19.8-26.0), 10% were overweight (BMI 26.1-29.0) and 22% were obese (BMI>29.0).

Table 3 provides a summary of maternal gestational characteristics. Women were diagnosed with GDM at an average of 32 weeks gestation. Women were initially classified at their first visit to the clinic as having impaired glucose tolerance, class A1 (diet) or class A2 (diet and insulin) gestational diabetes; however the classifications of 13% of the women changed during treatment. For the purposes of representing these diagnostic changes in the analyses the classification at delivery, as opposed to at the first clinic visit, was used. Nineteen percent of women had impaired glucose tolerance, while 44% had class A1 GDM; both were treated with diet alone. The remaining 37% had class A2 GDM and were treated with a regimen of diet and insulin; 56 of the 164 women within this group initiated treatment on diet alone and changed to diet and insulin at least three weeks after diagnosis.

The sample population consumed an average daily dietary intake of 2047 kilocalories (8600 kJ), 171 g carbohydrate, 99 g protein and 106 g fat; this represents a distribution of energy from the macronutrients of 34%, 19% and 47% respectively. The variable which defined the accuracy of the diet information (see Methods section C.2) as 'good', 'fair' or 'poor' was used to create a subset of women with only a 'good' rating of accuracy for all clinic visits. This subset was comprised of 254 subjects, after all records with one or more 'fair' or 'poor' ratings on diet accuracy were removed. Analyses of the mean intakes of all dietary components for this more accurate subset are shown in Table 4, and show that these women consumed 2062 kcal/d. The analyses in Table 4 which stratified by BMI and treatment categories will be discussed in later sections.

The mean weight gain at delivery was 12.8 kg (Table 3). Prior to diagnosis, at a mean gestational age of 32 weeks, women had gained an average of 11.3 kg, and during the 8 week treatment period women gained 1.4 kg. The rate of weight gain during treatment was 0.17 kg/wk, one-half of the pre-diagnostic rate of 0.35 kg/wk.

There are certain conditions, such as amniotic fluid volume disorders and preterm labor, which may arise during pregnancy more frequently among women with GDM.

Polyhydramnios is an excessive amount of fluid in the amniotic sac as determined by ultrasound or clinical evaluation; oligohydramnios is the opposite, that is a lower than normal amount of amniotic fluid. The frequency of each of these conditions was 6%. Preterm labor occurred in 11.7% of the population studied, and was controlled with a medication, Ritodrine and bed rest. As preterm delivery was one of the exclusion criteria, women delivering before 37 weeks were excluded from the study. The mean gestational length was 39 weeks; 87% were delivered of their infants between 37 and 39 weeks gestation (earlier than usual because of inductions)

Table 5 provides information on the labour and delivery. Labour was induced in 56% of the population. Sixty-seven percent of women delivered their infants vaginally, 20% of whom required either low or mid-forceps during delivery. One-third of the cohort were delivered of their infants by caesarean section, although only 19% had primary caesarean sections. Maternal morbidity during labour and delivery included varying degrees of laceration and dystocia as a result of the infant's delivery. Severe lacerations (uterine rupture, cervical and 4th degree perineal lacerations) occurred in 18 women. Shoulder dystocia occurs when the fetus' shoulders are unable to descend normally through the mothers' pelvis; the incidence of shoulder dystocia in this cohort was 2.3%.

A.2 Comparison of Body Mass Index groups

Table 6 shows the result of bivariate analysis of several variables according to prepregnancy BMI category. The underweight women were significantly younger than the other weight groups. There was no difference in height among the four groups. Total weight gain, net weight gain (total gain less birthweight and placental weight) and weight gain at diagnosis were significantly and inversely related to the women's pregravid BMI.

Prior to diagnosis the underweight, normal weight and overweight women were gaining weight at rates of 0.38, 0.37 and 0.34 kg/wk respectively. The rates of weight gain among the underweight and normal weight women were significantly higher than the obese women who gained at the rate of 0.28 kg/wk ($p<.0005$). The post-diagnostic rate of weight gain was significantly higher in the underweight women than in the obese women ($p<.02$). A comparison of the mean rates of weight gain before and after diagnosis of

GDM revealed a range of reductions of 26% to 68% with the institution of the diabetic diet. As illustrated in the Figure 4, this change was most marked in the higher BMI groups. The recommended rate of weight gain during the second and third trimester in normal pregnancy is 0.34 to 0.45 kg/wk (Health and Welfare 1987) and as there is no standard recommendation for rate of weight gain in GDM pregnancy the normal range is shown here for comparison. After diagnosis, 65% of the gestational diabetics gained below the recommended rate, including 26% of subjects who lost weight during treatment (Table 7).

Differences in dietary intake among the BMI groups (Table 6), were observed only with respect to energy according to the analyses of the whole sample; however Table 4 indicates that the more accurate subset consumed different levels of protein as well. Within this more accurate subset the heavier women consumed significantly more calories and grams of protein per day than the lighter women, although the differences were very small; the mean carbohydrate and fat intakes did not differ. Based on the pregravid body mass the energy intakes were very different among the groups (Table 6); they ranged from 24 kcal/kg in the obese women to 42 kcal/kg in the underweight women ($p<.0001$).

A significantly greater proportion of under and normal weight women were treated by diet alone compared with the overweight and obese women, who were more frequently treated by diet and insulin. Both fasting and post-prandial mean plasma glucose values during treatment were significantly higher in the heavier patients, although all met the criteria for optimal diabetic control for this clinic (fasting <5.0 mmol/L, 1 hr post-prandial <6.7 mmol/L).

Length of treatment refers to the period from diagnosis to delivery when the women were followed at the clinic. Treatment length was shorter for the underweight and normal weight women. Stratification by this variable indicated that treatment length was associated with several of the weight variables (Table 8). Women treated for GDM for 9 weeks or more were heavier prior to pregnancy and at delivery; they gained less weight weight prior to diagnosis and more weight during treatment than those treated for a shorter period.

Prepregnancy body mass index was not associated with the length of gestation, nor the proportion of women who had induced labour (Table 6). A greater percentage of overweight and obese women were delivered of their infants by caesarean section.

A.3 Comparison of treatment groups

Treatment with diet alone or diet and insulin was associated with many variables (Table 9). Gestational diabetics treated with diet alone were significantly younger, lighter and gained weight at a higher rate prior to diagnosis than their counterparts treated with diet and insulin. Total and net weight gain, and weight gain at diagnosis were significantly lower in the women treated with insulin. Rate of weight gain after diagnosis, frequency of smoking, and height were not different between the treatment groups. Within the subset of women with more accurate dietary data (Table 4) the energy intakes were not significantly different. The group treated with diet alone consumed more energy on the basis of pregravid body mass (kcal/kg).

Those treated with insulin had higher mean plasma glucose values and were diagnosed earlier in their pregnancy, as indicated by the longer treatment period; their length of gestation was shorter and they had a greater proportion of deliveries by caesarean section. The proportion of women who underwent induction of labor was not different between the treatment categories.

A.4 Ketonuria

Correlation analysis was done in order to evaluate if the presence of urinary ketones was associated with weight changes during treatment. Presence of ketonuria was recorded as none, mild, moderate or severe (for more detail see Methods section C 2). A variable was derived which calculated the change in weight between visits and was tested by correlation analysis with the presence of ketonuria reported during the same period.

Table 10 shows that during the week after the first clinic visit, 34% of subjects experienced ketonuria; 15% of those were at moderate to severe levels. The proportion with ketonuria dropped to 20% the next week, then leveled off to 8 to 10% of women having mild ketonuria between visits.

The Spearman ranked correlation coefficients and level of significance for the first ten visits were calculated using the presence and severity of ketonuria (Table 10). Correlation analysis included only the first ten visits since the number of observations at

each visit thereafter were too small for analysis. The table also provides the mean weight change and frequency of different levels of ketonuria at each visit upon which the correlation coefficients were based. There was significant correlation between the weight loss and the amount of ketones spilled in the urine during the week prior to the second and fifth visits. Correlation was close to conventional significance ($p<.05$) for these variables prior to the third ($p=.061$) and seventh ($p=.077$) visits as well.

A.5 Effect of treatment on plasma glucose

Fasting and post-prandial plasma glucose (PG) values at the first clinic visit were compared to the average of the remaining PG values during follow-up in order to assess how the initiation of treatment affected glycemia. Table 11 presents the results of this analysis for both the entire sample and the subset of women treated by diet alone. Treatment significantly reduced fasting and post-prandial PG for the entire cohort. When diet was the only intervention, mean fasting PG decreased from 4.36 to 4.09 mmol/L ($p< 0.0001$), and post -prandial PG did not change. Among the women treated by diet and insulin mean fasting PG decreased significantly from 5.46 to 4.50 mmol/L, and the post-prandial values decreased from 6.98 to 6.19 mmol/L ($p< 0.0001$). The goals for fasting and post-prandial glucose for this clinic are 5.0 and 6.7 mmol/L respectively.

B Infant Characteristics

B.1 Overview of the infant's anthropometric measures, morbidity and mortality

The anthropometric measurements of the neonates are shown in Table 12. The average birthweight was 3520 g, and ranged from 2170 g to 5085 g. The mean head circumference of the infants was 35.1 cm, and the mean body length was 51.2 cm. Placental weight, for which there were only 405 values, averaged 683 g.

Birthweight ratio is defined as the infant's birthweight divided by the mean birthweight expected for the infant's gestational age, and is based on established growth

curves (Usher and McLean 1969). The mean birthweight ratio was 1.06. Birthweight to placental weight ratio was derived by dividing the birthweight in grams by the placental weight in grams. The mean B:P ratio for the subset was 5.3 and ranged from 3.2 to 8.1.

Macrosomia means excessive growth, although clinically this term has been used to define a high birthweight. Some researchers define macrosomia as a birthweight of 4000 g (Boyd et al. 1983, Jacobson et al. 1989), others as a birthweight of 4500 g (Spellacy et al 1985, Mondanlou et al 1980), while some use the definition of a birthweight greater than the 90th percentile (Willman et al. 1986).

In an attempt to define macrosomia among this cohort the incidence of macrosomia at different intervals of birthweight and birthweight ratio was examined (Table 13). Thirty five percent (151) of the babies had birthweight ratios greater than 1.10; 22% (97) of all the infants had birthweight ratios of greater than 1.15, and 10% (44) of the infants had birthweight ratios at or above 1.25. Within the latter group 18% (8) of the infants weighed between 2501 and 3999 g, 52% (23) had birthweights between 4000 and 4499 g, 30% (13) had birthweight greater than or equal to 4500 g. All of the very heavy infants (>4500g) fell under the highest birthweight ratio category, and since that is the birthweight believed to be associated with negative consequences for the infant (Ales and Santini 1989), a birthweight ratio of greater than of equal to 1.25 was assigned to define macrosomia for the purposes of this study.

The frequency of infant morbidity and mortality is listed in Table 12. Plasma glucose (PG) was measured in 301 infants, and hypoglycemia defined as a PG<1.6 mmol/L (30mg/dL) was reported in 14 babies or 3.2% of the entire sample. Using another commonly used definition of hypoglycemia (<2.1 mmol/L or 40 mg/dL) to the newborns gave rise to a frequency of 38 infants or 8.7% of the whole sample. Hyperbilirubinemia (serum bilirubin>205 μmol/L or 12 mg/dL) was found 12.2% of the babies. Thirty-nine neonates had elevated hematocrit (>65%), known as polycythemia.

Birth trauma was reported for some of the infants. Three infants sustained fractured clavicles at birth, while 2 developed facial paralysis and another 2 had brachial paralysis; all of these conditions normally resolve during the neonatal period. There were 26 malformations identified among the neonates; they are listed in Table 14 and categorized as

either minor or major deformities. One infant died shortly after birth due to congenital malformations, which were described as: a single ventricle, and a tracheo-esophageal fistula. The mother of this infant had a pregravid BMI of 24.7 (normal weight group); she was 22 years old when she was diagnosed with class A2 gestational diabetes 34 days prior to delivery.

B.2 Comparison of infant characteristics by BMI categories

Significant differences were found in the bivariate analysis of infant characteristics by the maternal prepregnancy BMI categories (Table 15). Infants born to the overweight and obese mothers weighed more than the infants whose mothers were normal or underweight. The birthweight ratio (gestational-age adjusted birthweight) was also significantly higher among the heavier women. Placenta weight values were available for only 405 of the infants and were higher among the higher BMI categories. Stratification by BMI categories revealed that as BMI increased, birthweight-to-placental weight ratio decreased; this negative association was close to conventional statistical significance ($p=0.0578$).

B.3 Comparison of infant characteristics by treatment categories

Table 16 shows that babies born to mothers who received insulin during treatment weighed an average of 120 g more than those born to mothers treated by diet alone ($p< 0.0087$). The mean birthweight ratio and placental weight were also higher among those treated with insulin. Mean birthweight-to-placental weight ratio of women treated by diet was higher (5.33) than the ratio of those treated by diet and insulin (5.17); a difference which was close to statistical significance ($p=0.065$).

B.4 Comparison of maternal and infant characteristics by birthweight ratio categories

A birthweight ratio of less than or equal to 0.85 represented small-for gestational-age (SGA) babies (6.7%); a ratio of 0.86 to 1.10 indicated that the baby's birthweight was average-for-gestational-age (AGA) (58.7%); and a ratio of greater than 1.10 indicated a large-for-gestational-age baby (LGA) (34.6%). In Table 17, the bivariate analysis of

birthweight ratio categories and maternal factors associated with infant weight are shown.

The proportion of smokers among the women who gave birth to SGA babies was higher than those with AGA babies and LGA babies ($p<.02$). There was no difference between the mother's age or height among the different birthweight ratio categories.

Prepregnancy body mass index was significantly lower in the women delivered of AGA babies than those with LGA babies. The mothers of SGA infants also gained less weight prior to diagnosis. Weight gain during treatment was not different among the three groups.

The mothers who delivered LGA infants had more severe gestational diabetes as indicated by their higher mean plasma glucose values. Compared to the other birthweight ratio groups, the mothers of LGA babies were treated more frequently with insulin ($p<.001$). The mean daily intake of energy and macronutrients did not differ among the birthweight ratio groups. The LGA babies were delivered earlier, at a mean gestational age of 38.8 weeks compared to the SGA babies who were delivered at an average of 39.6 weeks gestation. However there was not a difference in frequency of induction of labor among SGA, AGA and LGA, and although the trend was in the expected direction, the mothers of the heavier babies did not have significantly more caesarean sections. The average birthweight to placental ratio was not different between the birthweight ratio categories.

Overall the mothers of the LGA infants were heavier prepregnancy; smoked less during pregnancy; ate fewer kilocalories/kg during treatment; gained more weight throughout pregnancy, including prior to diagnosis but not during treatment; they were more likely to take insulin, had higher mean fasting and post-prandial plasma glucose values, and had a shorter length of gestation.

B.5 Secular trends of maternal and infant characteristics

Bivariate analysis was done on numerous variables to evaluate the presence of secular trends which may have occurred over the 11-year study period. Variables were analyzed for each year of the study, except for the first four years which were collapsed to provide enough subjects for comparison ($n=51$).

Women who started treatment in 1983 or earlier consumed significantly less kilocalories/day than those who started at the clinic between 1986 and 1988 ($p<0.0001$); these women also consumed less kcal/kg than the women diagnosed in 1988 ($p<0.0012$), other years were not different in terms of energy intake. Mean fasting plasma glucose was higher during 1979-1983 than during 1987 and 1988 ($p<0.0001$); no other years were significantly different. The one-hour post-prandial value was significantly higher between 1979 and 1983 than in all other years thereafter. Mean birthweight was higher prior to 1984 compared with 1988 ($p<.0001$), otherwise there were no differences. Birthweight ratio was greater in the early period than in 1989 only. Analyses by the above method did not indicate a difference in proportion of women on diet alone versus diet and insulin over the 11 year study period.

C Predictors of Infant Birthweight

C.1 Multiple linear regression

Regression analysis was conducted on this sample to determine the extent and direction of the effect that several independent variables have on the dependent variables, birthweight and birthweight ratio. Birthweight ratio was used as an outcome variable to provide a more precise model, because it involves adjustment for gestational age with each infant's birthweight. The regression model with birthweight as the dependent variable controls for gestational age as it does for the other independent variables, which makes it less precise since this method relies on a good fit to the statistical model. Although birthweight ratio provides a more precise regression model, the regression coefficients for the birthweight model have more practical application in terms of providing grams of birthweight affected by each causal factor; for these reasons regression data tables include results of analyses with both outcome variables.

Correlation analysis was conducted to evaluate which covariates were highly associated and should therefore not be in the same regression model (Table 18). Variables were removed from the model if they were not statistically significant. A "core" set of significant control variables was determined and used to analyze the independent effects of

other variables entered into the model individually.

C.2 Whole sample N=436

Table 19 provides a summary of the univariate regression coeffecients and six selected regression models. The more detailed regression analysis results for these models and others are in Appendix VI (Tables 19a to 19l). Column 1 of Table 19 shows the regression coefficients for each of the independent variable for purposes of comparison with the full regression models in the next six columns.

Initially twelve independent variables were entered into a multiple regression model to determine their independent effects on birthweight and birthweight ratio. Column 2 (Table 19a) shows the results of this analysis. Gestational age, BMI, height, smoking, infant gender, mean fasting plasma glucose (PG), and rate of weight gain prior to diagnosis were found to be predictors of infant birthweight. The regression coefficient (ß estimate) provides the estimated amount and direction of change in birthweight per unit of each predictor (independent variable) listed. For example, for every additional day of gestation, birthweight will increase by about 11 g, and this value lies approximately between 5 and 17 grams of birthweight with 95% confidence (confidence interval= ß±2{standard error}). The following variables were removed because they were not significant: maternal age at diagnosis, treatment category, rate of weight gain during treatment, and mean daily energy intake. The dietary data of the whole sample was used, since the differences between the subset with good diet accuracy and the whole sample were minimal. As well the number of observations used in the regression would have been reduced to 254 from 436, and the p value could not have changed to a significant level from 0.9108 (as shown in Table 19a). Length of treatment was not significant by conventional measures (p=0.1334), however with a p value of less than 0.20 it was suggestive of an association with birthweight and so was used in later regressions. Level of education was not significant (p>0.40) when entered into the above model. Since the number of observations was reduced from 436 to 345 due to missing data on years of schooling, this variable was excluded and the above model was repeated without education level.

The next regression, shown in column 3 (Table 19b), included 9 variables which

accounted for 23.5% of the variation in birthweight. Length of treatment was not found to be a predictor of birthweight; however it was highly correlated with gestational age, BMI, and rate of weight gain prior to diagnosis.

Rate of weight gain before diagnosis was highly correlated with length of treatment ($r= 0.164$, $p<0.001$), and therefore the regression presented in column 4 (Table 19c) excluded rate of weight gain to distinguish the effect of length of treatment. After control for gestational age, BMI, height, smoking, infant gender, parity and mean fasting PG, length of treatment was inversely related to birthweight.

Because of the correlation of numerous variables a model was developed with five elements which were found to be consistent predictors of birthweight: gestational age (for birthweight model only), maternal height, prepregnancy BMI, smoking status, and infant gender, as shown in column 5 (Table 19d). This model accounted for 11.6% of the variation in birthweight and 8.9% of the variation in birthweight ratio. After controlling for these five predictors several variables were entered individually into the regression model. Column 6 and 7 present the results of multiple regression with the core model plus rate of weight gain prior to diagnosis and fasting plasma glucose respectively. Other results are shown in Tables 19g to 19l (Appendix VI). The covariates found to be significant determinants of birthweight and birthweight ratio were: days of treatment, total weight gain, pre-diagnostic weight gain and rate of weight gain, insulin dosage, and mean fasting and post-prandial plasma glucose. Whether treatment included insulin or not was a significant predictor for birthweight ratio only (Table 19f). Using the same model, rate of weight gain during treatment, and mean energy, carbohydrate, protein and fat intakes during treatment were not found to be predictors of birthweight. These regressions were redone in the subset of women with good accuracy for the dietary information (n=254) and the results were no different. The regression analyses described above were also repeated after excluding the second pregnancy of 23 women who appeared in the study twice; as the results were no different, these second pregnancies were included in subsequent analyses.

C.3 Regression analysis by body mass index categories

Body mass index was consistently a strong predictor in the analyses of the entire sample of

436 women, as well as in smaller defined subsets of women. In order to evaluate the strength and direction of predictors of infant birthweight among the lighter versus the heavier women, regression analysis was done for three different BMI categories: underweight (BMI <19.8), normal weight (BMI 19.8-26), and the overweight and obese together (BMI>26).

Within the underweight group of 52 women regression analyses yielded only two significant predictors of infant birthweight: maternal height and gestational length. Table 20 summarizes the results of seven multiple regression analyses of predictors of birthweight according to prepregnancy BMI; column 1 and 2 present the regression coefficients of the 245 normal weight women and columns 3 to 7 present the regression coefficients of analyses of the overweight and obese women. The more detailed regression tables (20a to 20c) are in Appendix VII and show the, significance level, and standard error for each variable. These results indicate that among the normal weight women the "core" variables: gestational length, body mass index, maternal height, smoking and infant sex are significant predictors of birthweight, which together accounted for 18% of the variation in birthweight (column 2), length of treatment was not predictive of infant birthweight after adjusting for the core variables. After control for these core variables, rate of weight gain prior to diagnosis is positively associated with birthweight, while maternal age and fasting plasma glucose were not associated with birthweight (column 1)

The results of the regressions of the heavier women are presented in column 3 (Table 20b), and indicate that significant predictors of infant birthweight among the overweight and obese women are smoking, rate of weight gain prior to diagnosis, and mean fasting plasma glucose; this model accounted for 25.9% of the variation in birthweight. Column 4 presents the core variables, which account for only 4.2% of the variation in birthweight aomng the heavy women. Length of treatment was found to be negatively associated with birthweight in the heavier women, after control for the core variables (column 5). When rate of weight gain before diagnosis was regressed against birthweight with no other independent variables except the intercept (column 6), 12.9% of the variation in birthweight was explained. Similarly fasting plasma glucose alone explained 11.8% of the varitation in birthweight in the heavier women (column 7) When

the obese women were studied alone using similar regression models (Table 20c, Appendix VII) the significant predictors of birthweight were rate of weight gain and fasting PG.

C.4 Subset of women treated with diet alone (n=272)

A linear regression model was applied to a subset of women treated by diet alone, and is shown in Table 21. By removing those treated with insulin, the treatment period can then represent the length of the restricted dietary regimen alone. After control for pregravid BMI, maternal height, smoking, infant sex, and mean fasting plasma glucose, length of treatment remained negatively associated with infant birthweight. Mean fasting PG was no longer a significant predictor of infant birthweight among women treated by diet alone and maternal height was less significant in the diet alone group ($p=0.0822$) than for the whole sample ($p=0.0069$).

The limited variability between subjects rendered the dietary components (energy, protein and carbohydrate) non-significant as predictors, however length of treatment for this subset may serve as a proxy for the effect of the length of dietary treatment on birthweight. Thus each day of treatment by diet alone reduced birthweight by 2.3 g, as shown in Table 21.

C.5 Predictors of mean fasting plasma glucose (n=436)

Multiple regression analysis was carried out on models with fasting plasma glucose (PG) as the outcome variable and various potential predictor variables. The results are shown in Table 22. Body mass index, maternal age, rate of weight gain prior to diagnosis and diagnosis at delivery were all predictors of fasting PG during treatment, and after control for these variables mean daily energy, carbohydrate, and protein intake were all negatively associated with PG. Fat intake was not significant in these regressions.

C.6 Logistic regression to evaluate factors influencing macrosomia

Macrosomia was defined as a birthweight ratio ≥ 1.25, as described earlier in section B.1. The incidence of macrosomia by this definition was 10.1%. Table 23 presents the

incidence of macrosomia according to the interval variables listed; significance was determined by the Chi-square test to determine if the frequency of macrosomia in the categories was by chance alone. Macrosomia occurred more often with higher BMI and fasting plasma glucose, but not with increasing levels of weight gain (p= 102) Multiple logistic regression was performed to identify predictors of macrosomia in this population (Table 24). The odds ratio and confidence interval were calculated for each parameter entered into the logistic model. The results indicated that the odds of having a macrosomic infant significantly increase with increasing BMI, weight gain prior to diagnosis, fasting PG, maternal age but not height.

Table 2. Maternal characteristics (n=436)

Characteristic	n	%
Maternal age (yrs)		
<20	5	1.1
20-24	46	10.6
25-29	121	27.8
30-34	146	33.5
≥35	118	27.1
Parity		
Nulliparous	173	39.7
Primiparous	152	34.9
Multiparous	111	25.4
Smoker during pregnancy (cig/day)		
Total	96	22.0
<10	34	7.8
10-20	45	10.3
>20	17	3.9
Race		
White	244	70.7
Black	21	6.1
Oriental	29	8.4
East Indian	25	7.2
Other	26	7.5
missing	91	
Years of schooling		
0 - 8	18	5.3
9 - 11	100	29.2
12-13	77	22.5
14-17	106	31.0
>17	41	12.0
unknown	91	
Alcohol consumed during pregnancy		
none	311	71.3
occasional	105	24.1
1 or more drinks/day	4	0.9
unspecified	16	3.7
Social drugs		
none	415	95.2
cannabis	5	1.1
unspecified	16	3.7
Prepregnancy BMI category		
Underweight (<19.8)	52	11.9
Normal (19.8 - 26.0)	244	56.0
Overweight (26.1 - 29.0)	44	10.1
Obese (>29.0)	96	22.0

Table 3. Maternal characteristics during treatment (n=436) [1]

Characteristic	n	%
Diagnosis at delivery (treatment)		
Impaired glucose tolerance (diet)	82	19.3
Class A1 (diet)	190	43.6
Class A2 (diet and insulin)	164	37.2
Mean gestational age at diagnosis (wks)	31.9 ± 5.0	
Mean dietary intake during treatment		
Energy (kcal/d)	2047±121	
Carbohydrate (g/d)	171±24	
Protein (g/d)	99±15	
Fat (g/d)	106±17	
Distribution of energy (%)		
Carbohydrate	34	
Protein	19	
Fat	47	
Mean weight gain (kg)		
Total	12.76 ± 5.61	
Prediagnosis	11.32 ± 5.74	
Postdiagnosis	1.44 ± 2.42	
Rate of weight gain (kg/wk)		
Pre-diagnosis	0.35 ± 0.17	
Post-diagnosis	0.17 ± 0.34	
Amniotic fluid volume disorders		
Polyhydramnios	26	6.0
Oligohydramnios	27	6.2
Preterm labor (without preterm delivery)	51	11.7
Gestational length (weeks)		
37	61	14.0
38	154	35.3
39	165	37.8
40	41	9.4
41	11	2.5
>41	4	0.9

[1] mean ± standard deviation, unless otherwise specified

Table 4 Dietary variables for those with good diet accuracy at 100% of the visits (n=254)

Susbet and variable	Daily Intake (mean ± std dev)
Whole subset	
Energy (kcal)	2062±124
Carbohydrate (g)	171±25
Protein (g)	99±15

By BMI categories	Underweight (<19.8) n = 37	Normal (19.8-26) n = 141	Overweight (26.1-29) n = 25	Obese (>29) n = 51	p value
Energy (kcal)	2049±97	2046±118	2085±176	2106±116	0.017
Carbohydrate (g)	170±25	168±24	174±24	178±26	n.s.
Protein (g)	97±14	97±15	103±17	105±15	0.012

By treatment categories	Diet only (n =172)	Diet and Insulin (n =82)	p value
Energy (kcal)	2055±120	2078±129	n.s.
Carbohydrate (g)	166±25	181±21	0.0001
Protein (g)	96±15	106±14	0.0001

Table 5. Characteristics of labor and delivery (N=436)

Characteristic	n	%
Mean gestational length (wks)	39.0 ± 1.0 [1]	
Labor induced	246	56.4
Delivery		
Vaginal, spontaneous	233	53.4
Vaginal: low-forceps	34	7.8
mid-forceps	24	5.5
Caesarean section		
primary	82	18.8
repeat	63	14.4
Maternal morbidity		
Laceration		
uterine rupture	1	0.2
cervical laceration	7	1.6
vaginal laceration	14	3.2
perineal: 1st degree	36	8.3
2nd degree	29	6.7
3rd degree	19	4.4
4th degree	10	2.3
multiple laceration	6	1.4
Dystocia	10	2.3

[1] mean ± standard deviation

Table 6. Variables according to prepregnancy body mass index category [1]

Variable	Underweight (<19.8) n = 52	Normal (19.8-26) n = 244	Overweight (26.1-29) n = 44	Obese (>29) n = 96	p value
Smoker (%)	19.2	21.2	22.7	25.3	>0.05.
Age at diagnosis	29.9±5.1	31.6±5.0	33.5±5.2	31.6±5.3	0.009
Height (cm)	1.60±.07	1.61±0.06	1.59±0.07	1.61±0.09	0.451
Weight gain (kg)					
Total	14.46±5.07	13.53±4.70	12.28±6.06	10.05±7.03	0.0001
Net [2]	10.20±4.67	8.75±5.23	6.87±6.58	4.91±7.25	0.0001
At diagnosis	12.72±4.59	12.10±4.82	10.97±6.24	8.72±7.31	0.0001
During treatment	1.74±1.69	1.44±2.25	1.30±2.55	1.34±3.03	0.771
Rate of gain (kg/week)					
Pre-diagnosis	0.38±0.15	0.37±0.15	0.34±0.19	0.28±0.24	.0005
Post-diagnosis	0.28±0.28	0.17±0.35	0.11±0.29	0.11±0.37	.02
Mean dietary intake					
Energy (kcal/d)	2047±117	2034±115	2061±149	2074±119	0.0365
Carbohydrate (g/d)	171±25	171±28	175±21	178±24	0.125
Protein (g/d)	98±14	98±15	102±15	102±15	0.100
Fat (g/d)	108±19	106±17	106±19	106±17	0.110
Diet per pregravid mass (kcal/kg)	42.3±4.5	34.8±3.6	29.9±2.8	23.9±3.8	0.0001
Treatment (%)					
Diet	84.6	71.4	45.5	34.7	0.0001
Mean blood glucose (mmol/L)					
Fasting	4.0±0.4	4.3±0.5	4.6±0.8	4.7±0.7	0.0001
1 hr post-prandial	5.7±1.1	5.9±0.9	6.1±0.8	6.4±1.0	0.0001
Treatment length (wks)	5.8±2.5	6.5±3.7	8.0±5.9	8.7±6.7	0.0001
Gestational length (wks)	38.9±0.9	39.0±0.9	39.1±1.1	38.8±1.0	0.150
Induced labor (%)	51.9	59.6	52.3	52.6	>0.05
Caesarean section (%)	28.9	30.2	38.6	41.1	.039

[1] mean ± standard deviation

[2] total weight gain less birthweight and placental weight

Figure 4. Comparison of Pre- and Post-diagnostic rate of weight gain by BMI categories

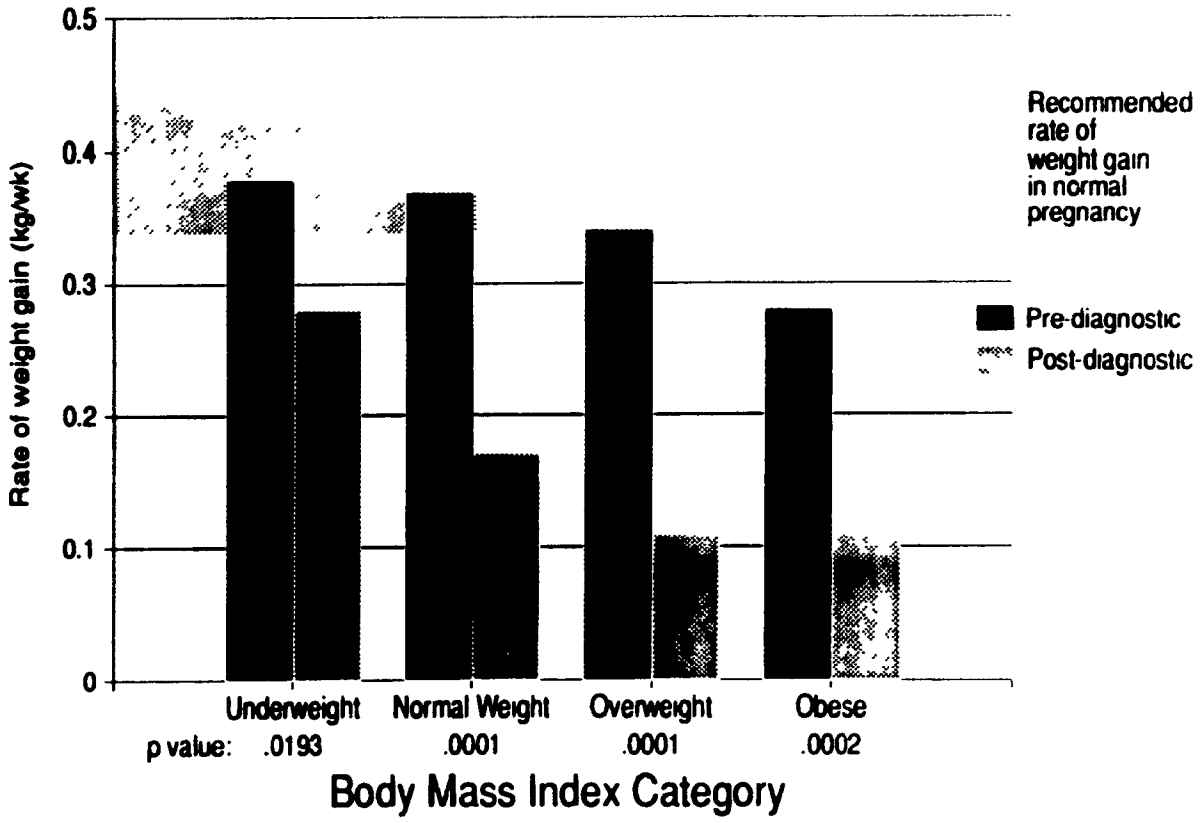


Table 7. Rate of weight gain after diagnosis

Class of rate of weight gain		Frequency	Percent
Very low	-1.4 to 0 kg/wk	112	25.7
Low	0 to 0.2 kg/wk	171	39.2
Normal	0.3 to 0.4 kg/wk	105	24.1
High	0.5 to 0.7 kg/wk	39	8.9
Very high	0.8 to 2.0 kg/wk	9	2.1

Table 8. Weight variables according to weeks of treatment

Variable (kg)	Weeks of treatment				p value
	< 4	4 to 5	6 to 8	9 or more	
Pregravid weight	63.80	64.88	62.14	69.90	.0025
Weight at diagnosis	77.27	77.15	73.20	78.44	.08 n.s.
Weight prior to delivery	77.48	77.87	74.82	81.61	.01
Weight gain prior to diagnosis	13.47	12.27	11.06	8.54	.0001
Weight gain during treatment	0.22	0.72	1.62	3.17	.0001

Table 9. Selected maternal variables according to treatment group [1]

Variable	Diet only (n =272)	Diet and Insulin (n = 164)	p value
Smoker (%)	23.4	19.8	>0.05
Age (years)	31.1±5.1	32.3±5.1	0.0176
Height (cm)	1.61±.08	1.61±0.06	0.977
Body mass index (kg/m^2)	23.8±5.2	27.7±6.4	0.0001
Weight gain (kg)			
Total	13.33±5.19	11.79±6.16	0.0054
Net [2]	8.44±5.82	6.97±6.33	0.0138
At diagnosis	12.20±5.17	9.83±6.34	0.0001
During treatment	1.13±1.98	1.96±2.94	0.0005
Rate of gain (kg/week)			
Pre-diagnosis	0.36±0.15	0.32±0.26	0.0087
Post-diagnosis	0.16±0.36	0.18±0.31	0.548
Mean dietary intake			
Energy (kcal/d)	2033±117	2069±123	0.0033
Carbohydrate (g/d)	168±24	182±21	0.0001
Protein (g/d)	96±15	104±13	0.0001
Fat (g/d)	109±18	103±15	0.0002
Diet per pregravid mass (kcal/kg)	34.3±6.2	30.3±6.8	0.0001
Mean blood glucose (mmol/L)			
Fasting	4.1±0.4	4.7±0.7	0.0001
1 hr post-prandial	5.7±0.8	6.5±1.0	0.0001
Treatment length (wks)	5.8±3.3	9.1±6.0	0.0001
Gestational length (wks)	39.1±0.9	38.8±1.0	0.0035
Induced labor (%)	58.8	52.5	>0.05
Caesarean section (%)	29.4	39.6	0.028

[1] mean ± standard deviation, unless otherwise specified
[2] total weight gain less birthweight and placental weight

Table 10. Spearman correlation analysis of weekly weight changes and ketonuria

Visit	Correlation coefficient	p value	Mean weight change	Presence of ketonuria (%) none	mild	mod	severe	N[1] observ.
2	-0.141	0.004	-0.14	66.4	17.5	9.2	6.9	423
3	-0.091	0.061	0.29	79.8	1.6	6.7	1.9	421
4	-0.039	0.457	0.28	86.3	7.8	5.7	0.3	371
5	-0.140	0.014	0.35	88.1	9.0	2.9	0.0	310
6	-0.014	0.830	0.31	89.6	8.8	1.6	0.0	251
7	-0.132	0.077	0.39	89.6	9.3	1.1	0.0	182
8	-0.082	0.342	0.34	92.8	6.5	0.7	0.0	139
9	0.000	0.999	0.34	90.5	8.4	1.1	0.0	95
10	-0.059	0.613	0.38	92.2	6.5	1.3	0.0	77
11	-0.084	0.537	0.39	91.2	8.8	0.0	0.0	57

[1] number of observations used in caluculations for each visit

Table 11. Comparison of plasma glucose at initial visit with remaining visits

	Mean	Median	Std dev	p value
All women, n=436				
Fasting PG (mmol/L)				
Initial visit	4.80	4.59	1.24	0.0001
Remaining visits	4.22	4.19	0.53	
Post-prandial PG (mmol/L)				
Initial visit	6.29	6.16	1.65	0.0001
Remaining visits	5.93	5.83	1.09	
Diet alone, n=272				
Fasting PG (mmol/L)				
Initial visit	4.36	4.37	0.60	0.0001
Remaining visits	4.09	4.12	0.42	
Post-prandial PG (mmol/L)				
Initial visit	5.76	5.80	1.21	0.3927
Remaining visits	5.72	5.70	1.04	
Insulin and diet treatment, n=164				
Fasting PG (mmol/L)				
Initial visit	5.46	5.10	1.54	0.0001
Remaining visits	4.50	4.46	0.59	
Post-prandial PG (mmol/L)				
Initial visit	6.98	6.53	1.81	0.0001
Remaining visits	6.19	6.01	0.93	

Table 12. Information on the infants (N=436)

Characteristic	n	%
Mean neonatal anthropometrics[1]		
Birthweight (g)	3520 ± 466	
Head circumference (cm)	35.1 ± 1.5	
Length (cm)	51.2 ± 2.5	
Placental weight (g)	683 ± 136	
Mean neonatal ratios[1]		
Birthweight[2]	1.06 ± 0.14	
Birthweight to placental weight	5.27 ± 0.84	
Infant sex		
Female	198	45.4
Male	238	54.6
Infant morbidity		
Hypoglycemia[3]	14	3.2
Hyperbilirubinemia[4]	53	12.2
Polycythemia[5]	39	8.9
Fractured clavicle at birth	3	0.7
Paralysis: facial	2	0.5
brachial	2	0.5
Malformations[6]	26	5.6
Infant mortality	1	0.2

[1] Mean ± standard deviation
[2] Infant birthweight divided by the standard birthweight for the infant's gestational age (Usher and McLean, 1969)
[3] Plasma glucose < 1.6 mmol/L (30 mg/dL)
[4] Serum bilirubin > 205 μmol/L (12 mg/dL)
[5] Hematocrit > 65%
[6] See Table 14 for occurrence and classification

Table 13. Frequency of macrosomia by birthweight and birthweight ratio (n=151)

Birthweight (g)	Birthweight ratio category >1.10 to 1.15	>1.15 to <1.25	≥1.25	Total
<4000	50	33	8	91
4000-4499	4	20	23	47
≥4500	0	0	13	13
Total	54	53	44	151

Table 14. Occurrence and classification of malformations (n=26)

Malformation	Classification	
	Minor	Major
Preauricular skin tag	4	
Malformed earlobes	1	
Supernumerary teeth	2	
Macrocephaly		1
Ulnar extra digit	2	
Unilateral club foot	1	
Bilateral club foot	1	
Foot deformity	1	
Hemangioma, flat	2	
First degree hypospadias	1	
Unspecified degree of hyposapdius	1	
Tetrology of fallot	1	
Naevi	2	
Syndactyly	1	
Trisomy 21, harelip, cleft palate, partial cryptorchidism		1
Single ventricle, tracheo-esophageal fistula [1]		1
Cleft palate, unspecified degree of hypospadius		1
Bilateral choanal atresia		1

[1] Neonate died

Table 15. Infant characteristics according to prepregnancy BMI category [1]

Variable	Underweight (<19.8) n = 52	Normal (19.8-26) n = 244	Overweight (26.1-29) n = 44	Obese (>29) n = 96	p value
Birthweight (g)	3411±513	3478±407	3629±452	3635±554	0.0045
Birthweight ratio[2]	1.03±0.15	1.05±0.13	1.09±0.41	1.11±0.17	0.0008
Placenta weight (g) (n=405)	670±157	664±117	722±135	732±154	0.0002
Birthweight to placental weight ratio	5.25±0.88	5.36±0.83	5.15±0.72	5.09±0.87	0.0578

[1] mean ± standard deviation
[2] infant birthweight divided by the standard birthweight for the infant's gestational age (Usher and McLean, 1969)

Table 16. Infant characteristics according to treatment group [1]

Variable	Diet only (n =272)	Diet and Insulin (n = 164)	p value
Birthweight (g)	3475±440	3596±498	0.0087
Birthweight ratio	1.04±0.13	1.10±0.16	0.0001
Placenta weight (g)	669±127	711±144.	0.0020
Birthweight to placental weight ratio	5.33±0.84	5.17±0.83	0.0672

[1] mean ± standard deviation

Table 17. Selected variables according to birthweight ratio categories [1]

	SGA (≤0.85) n = 29	AGA (0.86-1.10) n = 256	LGA (>1.10) n = 151	p value
Smoker (%)	37.9	24.6	14.6	0.002
Age at diagnosis	31.8±4.6	31.5±5.1	31.7±5.3	0.8881
Height (cm)	1.59±.06	1.61±0.06	1.61±0.08	0.3776
Body mass index (kg/m^2)	24.2±6.8	24.7±5.6	26.5±6.3	0.0056
Weight gain (kg)				
Total	9.94±3.34	12.22±5.58	14.21±5.68	0.0001
Net [2]	5.34±4.69	7.58±6.13	8.75±6.02	0.0155
At diagnosis	8.37±3.78	10.74±5.63	12.88±5.86	0.0001
During treatment	1.57±1.66	1.48±2.35	1.33±2.64	0.7876
Rate of gain (kg/week)				
Pre-diagnosis	0.25±0.11	0.33±0.18	0.40±0.18	0.0001
Post-diagnosis	0.21±0.33	0.17±0.34	0.14±0.36	0.5935
Mean dietary intake				
Energy (kcal/d)	2039±104	2046±118	2050±129	0.8821
Carbohydrate (g/d)	171±17	174±24	172±25	0.6019
Protein (g/d)	97±10	100±15	99±16	0.7656
Fat (g/d)	108±14	106±17	107±18	0.7324
Diet per pregravid mass (kcal/kg)	35.4±8.3	33.5±6.5	31.2±6.4	0.0004
Treatment (%)				
Diet	69.0	68.4	51.0	0.001
Mean blood glucose (mmol/L)				
Fasting	4.2±0.5	4.3±0.5	4.5±0.8	0.0001
1 hr post-prandial	5.7±1.0	5.8±0.8	6.4±1.1	0.0001
Treatment length (wks)	7.2±4.1	7.1±6.5	6.9±5.3	0.9041
Gestational length (wks)	39.6±1.4	39.0±0.9	38.8±0.9	0.0002
Induced labor (%)	44.8	59.0	54.3	>0.05
Caesarean section (%)	27.6	31.3	37.8	>0.05
Mean birthweight (g)	2753± 44	3329± 16	3991± 27	0.0001
Placenta weight (g) (n=405)	538±117	654±113	763±130	>0.05
Birthweight to placental weight ratio	5.20±1.00	5.21±0.79	5.36±0.88	0.0672

[1] mean ± standard deviation
[2] total weight gain less birthweight and placental weight

Table 18. Correlation analysis matrix of the predictor (independent) variables[1]

Variable (abbreviation)	GA	BMI	HT	AGE	KCAL	RATE	RATX	PG	INSUL	LNGTX	PARI
Gestational age (GA)	--	-0.054 0.263	-0.001 0.991	-0.041 0.393	0.005 0.918	0.048 0.321	-0.056 0.245	-0.003 0.958	-0.138 0.004	-0.101 0.036	-0.079 0.101
Body mass index (BMI)	--	--	-0.112 0.020	0.025 0.603	0.149 0.002	-0.243 <0.001	-0.142 0.003	0.335 <0.001	0.315 <0.001	0.167 <0.001	0.134 0.005
Height (HT)	--	--	--	0.062 0.197	0.234 <0.008	0.113 0.018	-0.105 0.029	-0.017 0.722	-0.002 0.963	0.029 0.550	-0.104 0.030
Maternal age (AGE)	--	--	--	--	0.078 0.104	-0.071 0.143	-0.078 0.103	0.003 0.958	-0.137 0.004	0.098 0.042	0.263 <0.001
Mean energy intake (KCAL)	--	--	--	--	--	-0.012 0.811	-0.078 0.103	0.009 0.852	0.141 0.003	0.098 0.041	-0.031 0.521
Rate of weight gain prior to diagnosis (RATE)	--	--	--	--	--	--	-0.032 0.504	0.087 0.069	-0.110 0.022	-0.164 <0.001	-0.188 <0.001
Rate of weight gain during treatment (RATX)	--	--	--	--	--	--	--	-0.043 0.369	0.025 0.608	0.164 <0.001	0.027 0.580
Mean fasting plasma glucose (PG)	--	--	--	--	--	--	--	--	0.467 <0.001	0.053 0.265	0.119 0.013
Treatment with insulin (INSUL)	--	--	--	--	--	--	--	--	--	0.357 <0.001	0.115 0.016
Length of treatment (LNGTX)	--	--	--	--	--	--	--	--	--	--	0.135 0.005
Parity (PARI)	--	--	--	--	--	--	--	--	--	--	--

[1]Matrix provides Pearson correlation coefficient / p value for each variable pair

Table 19. Multiple regression analysis summary for predictors of infant birthweight (grams)

Independent Variable	1 Univariate regression coefficients	2 Regression coefficient	3 Regression coefficient	4 Regression coefficient	5 Regression coefficient	6 Regression coefficient	7 Regression coefficient
Intercept		-1681.05	-1564.15	-1595.40	-1193.13	-1118.14	-1660.84
Gestational age (days)	10.97 ***	11.33 ***	10.93 ***	10.98 ***	11.59 ***	10.85 ***	11.38 ***
Body mass index (kg/m^2)	12.99 ***	16.73 ***	17.09 ***	11.51 **	16.03 ***	21.43 ***	10.55 *
Height (cm)	6.45 *	6.41 *	6.45 *	7.98 **	7.76 **	6.03 *	7.47 *
Parity	13.98	31.99	31.75	13.85	--	--	--
Smoker (no/yes)	-188.79 ***	-206.58 ***	-210.62 ***	-200.07 ***	-211.49 ***	-219.02 ***	-200.40 ***
Infant gender (f/m)	97.85 *	88.64 *	92.24 *	102.71 *	102.76 *	93.01 *	104.37 *
Received insulin (no/yes)	115.43 *	51.34	--	--	--	--	--
Days of treatment	-0.99	-1.25	-0.99	-1.28 *	--	--	--
Mean fasting PG (mmol/L)	194.53 ***	96.02 *	113.42 **	156.78 ***	--	--	159.40 ***
Rate of weight gain prior to diagnosis (kg/wk)	706.99 ***	784.80 ***	773.56 ***	--	--	833.19 ***	--
Rate of weight gain during treatment (kg/wk)	-84.98	14.80	--	--	--	--	--
Mean daily energy intake (kcal/d)	0.18	0.017	--	--	--	--	--
R square	--	**0.237**	**0.235**	**0.162**	**0.116**	**0.205**	**0.153**

*p value < 0.05, **p value<0.01, ***pvalue<0.001
-- indicates variable not included in model

Table 20. Multiple regression summary for predictors of infant birthweight (grams) according to prepregnancy BMI

Independent Variable	1 Non-obese[1] regression coefficient	2 Non-obese Regression coefficient	3 Obese[2] Regression coefficient	4 Obese Regression coefficient	5 Obese Regression coefficient	6 Obese Regression coefficient	7 Obese Regression coefficient
Intercept	-1943.15	-2430.62	1260.16	1514.32	2096.95	2487.38	3385.85
Gestational age (days)	8.80 *	9.71 **	6.99	9.16	6.70	--	--
Body mass index (kg/m^2)	40.70 **	39.28 **	5.47	3.07	2.76	--	--
Height (cm)	10.88 **	14.84 ***	-2.04	-1.16	0.19	--	--
Maternal age	-1.96	--	-6.33	--	--	--	--
Smoker (no/yes)	-196.69 ***	-198.10 ***	-219.91 *	-188.75	-171.58	--	--
Infant gender (f/m)	138.28 **	148.16 **	-44.17	-32.00	-40.76	--	--
Days of treatment	--	-0.31	--	--	-2.15 *	--	--
Mean fasting PG (mmol/L)	39.07	--	204.35 ***	--	--	245.95 ***	--
Rate of weight gain prior to diagnosis (kg/wk)	705.91 ***	--	710.24 ***	--	--	--	813.77 ***
R square	**0.238**	**0.180**	**0.259**	**0.042**	**0.074**	**0.118**	**0.129**

[1]Non-obese = women with normal prepregnancy BMI
[2]Obese = women with overweight and obese prepregnancy BMI
*p value<0.05, **p value<0.01, ***pvalue<0.001

Table 21. Multiple regression analysis of women treated by diet alone (n=274)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.171		0.105	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-2576.749	0.0351	1216.44	0.6786	0.0005
Gestational age	16.934	0.0001	3.76	-	-
Body mass index	13.417	0.0075	4.98	0.0035	0.0219
Height (cm)	5.972	0.0822	3.42	0.0015	0.1402
Smoker	-205.368	0.0006	59.47	-.0551	0.0022
Infant gender	129.614	0.0114	50.87	0.0431	0.0050
Parity	15.506	0.4685	21.36	0.0046	0.4750
Mean fasting BG	67.416	0.2875	63.24	0.0157	0.4092
Days of treatment	-2.302	0.0596	0.596	-.0007	0.0483

Table 22. Multiple regression analysis of predictors of fasting glycemia

Independent variable	Regression coefficient	p value	Standard error	R square
model 1				
Intercept	3.091	0.0001	0.439	0.292
1. Body mass index	0.030	0.0001	0.004	
2. Age at diagnosis	0.014	0.0030	0.005	
3. Rate of weight gain prior to diagnosis	0.707	0.0001	0.145	
4. Diagnosis at delivery	0.301	0.0001	0.035	
5. Energy intake (kcal/d)	-.0004	0.0422	0.0002	
model 2				
1, 2, 3, 4, plus Carbohydrate intake (g/d)	-.0023	0.0296	0.0010	0.293
model 3				
1, 2, 3, 4, plus Protein intake (g/d)	-.0034	0.0452	0.0017	0.292
model 4				
1, 2, 3, 4, plus Fat intake (g/d)	0.0007	0.6172	0.0014	0.286

Table 23. Incidence of macrosomia according to selected maternal characteristics

Characteristic	n	%	Chi square	p value
Prepregnancy BMI				
<19.8	3	6.8	18.061	0.001
19.8 - 26.0	14	31.8		
>26 - 29.0	7	15.9		
>29.0	20	45.5		
Total weight gain (kg)				
<9	6	6.6	5.452	0.102
>9 -12	9	7.4		
>12 - <15	9	9.6		
≥15	20	15.4		
Fasting plasma glucose				
<4.0 mmol/L	8	7.6	11.105	0.001
4.0 - 4.4	7	4.0		
4.5 - 4.9	17	14.9		
≥5.0	12	29.3		

Table 24. Multiple logistic regression of maternal factors influencing the incidence of macrosomia

Variable	ß Estimate	Odd's Ratio	95% Confidence Interval	Chi square	p value
Intercept	9.4596				0.2935
Gestational length	-0.0902	0.914	{0.862, 0.969}	9.14	0.0025
Body mass index	0.0964	1.101	{1.042, 1.163}	11.76	0.0006
Height	0.0389	1.04	{1.009, 1.091}	2.57	0.1090
Weight gain prior to diagnosis	0.1047	1.110	{1.049, 1.175}	13.05	0.0003
Fasting plasma glucose	0.6064	1.834	{1.112, 3.025}	5.64	0.0175

Part IV

Discussion

Predictors of infant birthweight in normal pregnancy have been extensively studied, and those established as having a causal effect on birthweight include: gestational age, pregravid body mass index, maternal height, smoking, infant gender, gestational weight gain, maternal age, parity and socio-economic status (Kramer 1987). Of these variables, this study showed that the first six were predictors of birthweight in gestational diabetes; in addition to glycemia, length of treatment and severity of gestational diabetes. However the predictors of birthweight in GDM change among BMI groups, such that among the normal weight women glycemia and length of treatment are not associated with birthweight, and in the heavier women with GDM only weight gain, smoking, glycemia and length of treatment are predictors of birthweight. These changes in predictors of infant birthweight are summarized below.

Normal	**Gestational Diabetic Pregnancy**		
Pregnancy	**Whole Sample**	**Non-obese**	**Obese**
Prepregnancy BMI	Prepregnancy BMI	Prepregnancy BMI	--
Maternal height	Maternal height	Maternal height	--
Maternal age	--	Maternal age	--
Parity	--	--	--
Socioeconomic status	--	--	--
Weight gain	Weight gain	Weight gain	Weight gain
Smoking	Smoking	Smoking	--
Infant gender	Infant gender	Infant gender	--
Gestational length	Gestational length	Gestational length	--
--	Fasting PG	--	Fasting PG
--	Length of treatment	--	Length of treatment

Energy intake and rate of weight gain during treatment were not significant predictors of birthweight. The predictors of birthweight in GDM pregnancy will be discussed, followed by the implications for future research.

Prepregnancy body mass index

Regression analysis determined that prepregnancy body mass index (BMI) was a strong

predictor of infant birthweight, after control for gestational age, maternal height, smoking infant gender fasting plasma glucose and rate of weight gain before diagnosis This finding is consistent with other studies involving GDM pregnancy (Jacobson et al 1989 Maresh et al.1989) and normal pregnancy (Abrams and Laros 1986, Mitchell and Lerner 1989) BMI was also positively associated with fasting plasma glucose, which supports the notion that the heavier women have more severe diabetes.

Further regressions were performed to determine if the predictors of birthweight were the same among different BMI categories The analyses showed that for women with GDM, predictors varied according to BMI Among the overweight and obese women the predictors of birthweight were rate of weight gain prior to diagnosis fasting plasma glucose, and length of treatment, after adjusting for gestational length, BMI, height, smoking, infant gender and maternal age. Rate of weight gain alone accounted for 12.9% of the variation in birthweight for the overweight and obese sample, and the ß estimate indicated that for every additional 0.1 kg gained per week prior to diagnosis birthweight increased by 81 g. Among the obese women alone with GDM rate of weight gain prior to diagnosis remained a strong predictor of birthweight. This result is contrary to the compelling evidence of Abrams and Laros (1986) which showed that in normal pregnancy the weight gained by obese women during pregnancy does not contribute to increased birthweight. Our study also showed that among the overweight and obese women, each additional day of treatment decreased birthweight by 2.2 g; over a one month period that reflects a reduction in birthweight of 66 g due to length of treatment alone. These women delivered 61.4% of the macrosomic infants (birthweight ratio ≥ 1 25) The clinical message from these findings is to diagnose and initiate treatment of the heavier women as soon as possible to reduce the risk of excessive fetal growth.

Among the normal weight women regression analyses revealed that after adjusting for the same covariates listed above, rate of weight gain prior to diagnosis was also a strong predictor of birthweight. These findings, on weight gain in normal weight women with GDM, support the study of Abrams and Laros (1986) in relation gestational weight gain in this weight group influencing birthweight.

Only gestational age and height were predictors of birthweight in the regressions

involving the underweight women however, it is very likely due to the small number of observations within this group (n=52). Abrams and Laros (1986) showed a significant impact of BMI and weight gain among underweight women in normal pregnancy, from regression analysis involving 268 underweight women.

Logistic regression determined that increasing BMI increases the likelihood of having a macrosomic infant. For example an increase in BMI from 23 to 30 kg/m^2, doubles the odds that a woman would have a macrosomic infant, after controlling for gestational length, height, rate of weight gain prior to diagnosis and glycemia.

Glycemic control

Regression analyses which were done on the whole sample and stratified by BMI categories indicated that plasma glucose (PG) is a strong predictor of infant birthweight but only for the heavier women. For example among the overweight and obese women, each increase of fasting PG by 0.1 mmol/L will result in an increase in birthweight of about 20 g, independent of the effects of gestational length, BMI, height, smoking, and infant gender. If an overweight woman's mean fasting PG was 5.4 mmol/L rather than the mean of 4.6 mmol/l (1 standard deviation greater), her infant's birthweight would be 160 g higher, if all other factors remained the same. Among the normal weight women fasting plasma glucose was not a predictor of infant birthweight, after controlling for gestational length BMI, height, smoking, infant gender, maternal age, and gestional rate of weight gain prior to diagnosis. Fasting PG also signifcantly increases the odds of having a macrosomic infant (birthweight ratio $\geq$ 1.25); if PG increases by 1.0 mmol/L a women's odds of having a macrosomic infant are almost 2 times greater (odd's ratio=1.8). Evidently accelerated fetal growth is stimulated by higher plasma glucose levels, although this relationship appears to be dependent on maternal size; or there may be a threshold for the fetus' susceptability to PG, since the lighter women had lower mean plasma glucose levels.

Regression analysis to determine predictors of fasting PG indicated that BMI, maternal age, rate of weight gain before diagnosis and severity of GDM were positively associated with infant birthweight and after contol for these variables mean energy intake during treatment was negatively associated with PG. This inverse association could be

related to the strong effects of the other covariates, or to the variables not fitting well to the regression model. As well, the association between the predictor (kcal/d) and the outcome (PG) was reversed during treatment, whereby the plasma glucose levels were used to determine modifications in dietary intake, which subsequently influenced PG. Therefore the mean dietary intake was likely a marker for severity of GDM, since the women with more restricted diets had higher PG levels.

Insulin dosage was not a significant parameter in the regression analysis of birthweight within the entire cohort, but did reach significance in the analyses including only the heavier women. This variable likely acts as a marker of severity of diabetes and probably should not be interpreted as a clinical predictor of infant birthweight. The regression coefficient indicated that an increase in insulin dosage independently increased birthweight. However, despite the fact that maternal insulin does not cross the placenta to the fetus (Freinkel 1980), it is metabolized by the placenta and the role of insulin in placental processing of maternal nutrients is unclear (Hollingsworth 1985). Hence there may be some physiological significance to insulin levels influencing birthweight.

Diet

For the purposes of the discussion the dietary values for the subgroup with only good diet accuracy will be used. However the regression analyses which included mean daily energy intake used the diet values of the whole sample, since the mean values of the diet variables were quite similar it is unlikely that the more accurate group could have affected the p value of 0.9108; as well the number of observations used for the regression would have been reduced from 436 to 254.

The daily energy intake was very similar among the women followed at the GDM clinic, with a mean and standard deviation of 2062 ± 124 kcal/d. The heavier women consumed significantly more energy (by 50 kcal/d) than the lighter women, and the intakes of those treated with diet alone did not differ from those treated with insulin and diet. The mean energy intake was below the National Guidelines for Nutrition in Pregnancy, which recommends 2300 kcal/d during the second and third trimester for women aged 19-24, and 2200 kcal/d for women greater than 24 years of age (Health and Welfare Canada 1987).

The American Diabetes Association (ADA) (1985) recommends the same energy levels for GDM as for the non-diabetic pregnant women of normal weight, that is 35-38 kcal/kg of prepregnancy ideal body weight in order to promote a normal weight gain of 10.9-12.7 kg (24 to 28 lb). It is surprising that the GDM women of healthy weight that we studied consumed 35 kcal/kg during the treatment period, very close to the recommended amount, and yet they gained only 0.17 kg/wk for the last 8 weeks of gestation, compared to the goal of 0.3 to 0.4 kg/wk in normal pregnancy. From this assessment of actual dietary intake by means of weighed food records, it would appear that the recommended energy intake may be inadequate to support the expected rate of fetal growth. The additional energy requirements for pregnancy (300 kcal/d) are based on theoretical calculations (Hytten 1980). Some research involving actual dietary intakes which were closely monitored have contradicted these requirements. Part of a multinational study indicated that an increase of only 50-150 kcal/d is adequate to support normal weight gain (Durnin et al 1985). The Montreal Diet Dispensary on the other hand supplements diets of disadvantaged women with at least 500 kcal/d to improve gestational weight gain and birthweight (Rush 1981). Restricting energy intakes in order to limit weight gain is not an explicit goal of the diabetic clinic we studied, however if such restrictions contributed to better glycemic control then perhaps they are appropriate for the GDM population; although the presence of ketonuria may indicate that the restrictions are too severe. In the normal population the recommended energy levels have been disputed and should be re-evaluated.

The American Diabetes Association (ADA 1985) also recognized that some research indicates that caloric restrictions of 25 kcal/kg for obese pregnant women with GDM has improved maternal glycemic control without an unacceptable level of ketonuria (Jacobson et al 1989, Algert et al 1989, Langer 1989). This study population consumed a range of 23 kcal/kg among the obese to 42 kcal/kg for the underweight women, but it was not reported if these restrictions were without an unacceptable level of ketonuria. There is no consensus about what is acceptable in terms of frequency and degree of urinary ketones. In this study over the first 2 months of treatment the gestational diabetics had the presenece of ketonuria over 4 one-week periods, which was correlated with weight reduction in amounts that were significant or close to significant. Ketonuria was present among these women, and

although it is not yet clear if the impact of ketones on the fetus is harmful, beneficial or benign, it cannot be said that these women are energy restricted without maternal lipid stores being catabolized as a source of glucose due to an energy restricted diet.

The macronutrient composition of the diet consumed (34% carbohydrate, 19% protein, 47% fat) is strikingly different than the current recommendations for energy distribution (50%, 20%, 30% respectively) for the non-pregnant non-diabetic population. For normal pregnancy the distribution of macronutients has not been defined (Health and Welfare 1989). Recommendations for the GDM population vary; the ADA Committee on Food and Nutrition (1979) recommend that for pregnant diabetics 50-60% of energy come from carbohydrate, 20% from protein and 20-30% from fat. The use of low-carbohydrate, high-fat diets at this GDM clinic continues to be employed, with the belief that it reduces and maintains plasma glucose, and prevents significant ketonuria. Carbohydrate foods were distributed throughout the day at meals and snacks, but in limited quantities, while more fat or high-fat protein foods are added to the diet to resolve persistent ketonuria or to increase energy when needed. In this way actual energy intake remained moderately low and diabetic management goals were met. Some studies have prescribed very low energy diets (1200-1800 kcal/d) to accomplish tight glycemic control (Gillmer et al. 1986, Algert et al. 1985, Magee et al 1990) without evaluating or discussing the effect of manipulating the macronutrient distribution of energy; nor do these studies indicate how dietary compliance to the prescribed regimens was monitored.

The diets which the women consumed after diagnosis of GDM resulted in 50% reduction of rate of weight gain, 0.35 to 0.17 kg/wk (p value=0.0001). Significant reductions in rate of weight gain also occurred among all the prepregnancy BMI categories, although the reduction was less among the underweight women (26%) compared to the overweight women (68%). Daily energy intake during treatment was not correlated to weight gain during treatment (Pearson correlation coefficient -0.071, p=0.139); this is a common observation in research involving these variables and is related to energy expenditure not being accounted for as part of energy balance (Kramer 1987). However in the great majority of women activity did not increase; and often decreased during treatment, for example when the demands of the treatment protocol sometimes necessitated that the

women stop work, or when women went on partial or full bed rest to control preterm labor. Hence the reduction in weight gain may be attributed to a reduction in energy intake, as opposed to an increase in energy expenditure.

The impact of diet treatment without insulin was also found to be important in reducing fasting plasma glucose from an initial mean of 4.4 to a mean of 4.1 mmol/l during the remaining treatment period, which is indeed one of the goals of the dietary management. Although post-prandial PG was not reduced significantly with diet management: initial mean of 5.76 versus 5.72 mmol/L during the remaining treatment period, it was still well below the diabetic criteria of 6.7 mmol/L.

Multiple regression analysis indicated that mean energy intake was not a predictor of infant birthweight. However, when diet was the only intervention (n=272), length of treatment was negatively and independently associated with infant birthweight, after control for gestational length, BMI, height, smoking, and infant gender. The mean birthweight of infants born to this group of women was 3475 g. A reduction of 2.3 g in birthweight for each day of treatment, indicates that the length of the dietary treatment can play an independent role in preventing excessive fetal growth. Dietary management of GDM decreases the rate of weight gain and reduces fasting glycemia; the longer this treatment is applied the lower the infant birthweight.

Weight gain

Recommendations for weight gain during pregnancy differ for women of different pregravid body masses according to the National Guidelines for Nutrition in Pregnancy (Health and Welfare 1987); they specify that underweight women gain 13-15 kg, "healthy" weight women gain 10-14 kg and obese women gain 7-9 kg. The patterns of total weight gain of the GDM women were significantly different among the BMI categories. Comparison with the recommended patterns according to prepregnancy mass (IOM 1990) indicated that the underweight women gained within the recommended range from diagnosis to delivery; the normal weight women gained along the upper edge of the normal range during treatment, and the heavier women gained well above the recommended range

for their weight category. If only the mean total weight gain during pregnancy was reported the results could be misleading, since it appears that the women's weight gain was within the recommended normal range of 10 to 14 kg. Jacobson et al. (1989) reported a mean total weight gain of 13.7 kg among 97 women with GDM and Langer et al. (1989) reported a total gain of 14 kg; neither study stratified the results according to BMI in bivariate or regression analyses to separate the effects of these two potent predictors of birthweight. Total weight gain was a predictor of birthweight in this cohort, as has been found in some other studies of GDM pregnancy (Jacobson et al 1989, Langer et al 1989) and in normal pregnancy (Kramer 1987). Weight gain prior to diagnosis was also a strong predictor of birthweight, which indicated that for every additional kg of weight gained before diagnosis birthweight would increase by 27.1 g, very similar to the 26.9 g increase in birthweight for each kg of total weight gain. Multiple logistic regression showed that the rate of weight gain prior to diagnosis was a factor in increasing the likelihood of having a macrosomic infant.

Multiple regression analysis indicated that the rate of weight gain during treatment was not associated with infant birthweight, and this may also be attributed to the limited inter-subject variability. However the rate of weight gain prior to diagnosis was a strong predictor of infant birthweight; for every additional 0.1 kg gained per week birthweight increased by 83 g, after adjusting for gestational length, BMI, height, smoking, and infant sex. Once diagnosed the women's rate of weight gain fell from a mean of 0.35 to 0.17 kg/week; a reduction of 50% and a level well below the recommended rate of 0.34 to 0.45 kg/wk. If a woman continued to gain weight at the pre-diagnostic rate during the 9 weeks of treatment, birthweight certainly would have been higher.

The change in rate of weight gain after diagnosis is important biologically. The third trimester is the period of maximal fetal growth and is therefore the time when the fetus is most susceptible to energy restriction (Kramer 1987). Although treatment seems to have been growth limiting for the fetus, it may have only reduced excessive fetal growth. Trans-placental transfer of nutrients to the fetus was occurring, as the babies were monitored for normal growth by means of ultrasonography and abdominal measurements. However the fetus' rate of weight gain may have been reduced simultaneously with the mother's; clearly this would vary greatly with both fetal and maternal size. Many of the women were

reported to have large-for-gestational-age (LGA) fetus' when they started at the clinic; if treatment length was long enough, fetal growth rate was reduced by 1-2 standard deviations to a weight appropriate-for-gestational-age prior to delivery

Although it was hypothesized that the rate of weight gain during treatment would affect infant birthweight, the potential cause-effect relationship between rate of weight gain and birthweight could have been reversed by virtue of monitoring of fetal growth during treatment. If a fetus is diagnosed as LGA by ultrasound, energy intake may be reduced as a means of tighter glycemic control, the goal being to decrease the amount of metabolic fuel (glucose) being supplied to the fetus, thereby curbing it's growth rate. Essentially fetal weight, which soon becomes birthweight, influences treatment which affects birthweight and hence the causal path has been distorted.

In this study gestational weight gain clearly has a positive effect on fetal growth, but not during treatment of gestational diabetes.

Strengths of the study

This study involved women followed at a diabetic clinic within a large teaching hospital in a metropolis centre, which serves the entire community. High-risk referrals are received from distant regions, such as northern Quebec and the eastern provinces. As a result this cohort of 436 women represented a range of ethnic and socio-economic backgrounds.

Since it's origin in 1978, the RVH Antenatal clinic has employed a consistent and intensive approach to the treatment of GDM. This feature contributes to the high quality of data available for analysis.

A large dataset was collected from the clinic charts and the reputable MOND system, which permitted a comprehensive examination of the predictors of birthweight in this high risk population. To the best of our knowledge, this is the first time dietary intake during treatment of GDM, and gestational weight gain before and after diagnosis were characterized and evaluated for their effects on birthweight. An additional novel aspect of the study is that the effect of dietary management on gestational weight gain and glycemic control were described.

Limitations of the study

The determination of certain variables, such as gestational weight gain and body mass index utilized self-reported measures of both prepregnancy weight, which tends to be under-estimated, and maternal height, which tends to be over-estimated (IOM 1990). Since these measures are negatively and positively biased, weight gain may represent an overestimate and prepregnancy BMI could reflect an underestimate.

The inherent difficulty of assessing dietary data, exists in this study since we do not know with absolute certainty that the women recorded their actual intake versus what their prescibed diet. However there are many factors which we believe contribute to the quality of the data, and we do know the women reduced their intake since weight gain decreased.

Evaluation of the impact of energy intake on weight gain necessitates control for energy expenditure; reliable data were not available on activity levels among this cohort, however as discussed it is reasonable to assume that the energy expenditure of the majority of women studied did not increase after diagnosis, and it may have decreased. The weight gains calculated during the treatment period may represent over-estimations for some women, since peripheral edema which was noted clinically could not be translated into a weight factor for the purpose of analyses.

Although this study controlled for the most important confounding variables, there were a few of those identified by Kramer (1987), which were not controlled for in this study: maternal race, episodic illness, and the mother's birthweight. The population studied was predominantly white (at least 71%), and whites deliver infants of higher birthweight than Blacks, Pakistanis and Indians (Eastern). Since race was not controlled in the multivariate analysis it may limit the generalizability of these findings to a population with a similar racial distribution

Implications of study for clinical practice and future research

It is evident that prepregnancy body mass index exerts a strong influence on the extent to which nutritional and other treatment-related predictors affect birthweight. These inter-relationships will be considered below with respect to potential research questions.

The underweight and normal weight women gained more weight during pregnancy

and ate more kcal/kg, but their dietary management was still restrictive enough to bring about significant reductions in rate of weight gain and fasting glycemia. However neither rate of weight gain nor fasting PG were predictors of infant birthweight in these weight groups, nor was length of treatment a predictor. The lighter women were at lower risk of having heavy babies. The mean birthweight was well within the normal range, and was significantly lower among babies of the normal weight and underweight women than those who were heavier. The clinical question which remains with these facts in mind is, does the dietary management of these women need to be so tight? It may be more appropriate for the lighter women who have lighter babies to consume more energy (kcal/day), even though it may result in an increase in fasting PG and rate of weight gain during treatment. Since fasting PG was not a determinant of birthweight, within the range observed in this study, a representative calculation cannot be made. However among the whole cohort, when fasting PG was a predictor, it would take an increase of 1.0 mmol/L of PG to increase infant birthweight by only 113 g (Table 19, column 3).

The other question which follows from the evidence that dietary management does affect infant birthweight, is: could some of the women who are treated with insulin be managed by diet alone? In other words are the PG criteria for initiation of insulin too low? Insulin does not directly reduce infant birthweight, but rather reduces PG which was positively associated with birthweight and only among the overweight and obese women with GDM. It seems that dietary management alone may be appropriate for a greater proportion of the non-obese women, which indicates that these women require different criteria for the initiation of insulin than the obese women who have more severe diabetes.

The cost-benefit of current practices could be compared, since GDM management protocols (for initiation of insulin, degree of follow-up, dietary restrictions) vary between centres. The clinical practice changes discussed could potentially reduce health care costs with respect to reducing staff time. For the women with GDM, the question of the necessity of such intensive demands needs to be addressed; the direct costs (insulin, babysitters, travel, possibly leaving a job) and the indirect costs to these women (stress of leaving a job, being classified as having a high risk pregnancy and following a rigorous treatment protocol) are substantial. If diet alone can achieve similar results for certain

women, the use of insulin needs to be justified

Epidemiological studies are needed to investigate the impact of changes in treatment protocol on maternal and infant outcome A randomized trial of two levels of criteria for initiation of insulin among women with prepregnant BMI's in the underweight and normal weight categories, may illuminate the consequences for the mother and infant of more dietary control alone in the management of GDM Much of the early literature on GDM indicated that the infants of GDM mothers are at increased risk of negative consequences related to macrosomia, including birth trauma from shoulder dystocia, and postnatal hypoglycemia, hyperbilirubinemia, and polycythemia. However many of these findings were refuted when the designs and analyses of these studies were carefully scrutinized (Ales and Santini 1989, Hunter and Keirse 1989). These authors suggested that more recent evidence indicates that significant morbidity among infants of women with GDM occurs only when birthweights are 4.5 kg or more. Perhaps there is too much emphasis on normalizing birthweight, and not enough on how dietary and/or insulin treatment makes a difference to pregnancy outcome.

Conclusion

In conclusion, the findings of this study have implications for both clinical practice and future research endeavors. The important role that diet can play in reducing plasma glucose and modulating weight gain, may be undermined by aggresive insulin therapy. It appears that a rebalancing of the emphasis of gestational diabetes management is indicated, away from the absolute criteria for glycemic control for all women, towards the consideration of numerous other factors involved in achieving a healthy pregnancy outcome for mother and child, particularly the women's prepregnancy weight, but also gestational weight gain and time to delivery. Well-designed studies which address such changes in approach to treating gestational diabetes may have a significant contribution for women who develop this condition in the future.

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Appendices

Appendix I

White's Classification of Diabetes in Pregnancy[1]

Class A	Abnormal glucose tolerance test. Asymptomatic. Diet alone can maintain normoglycemia
Class B	Adult onset (age ≥ 20) and short duration (<10 years).
Class C	Early onset (age 1-19) or long duration (10-19 years)
Class D	Onset under age 10 or very long duration (≥20 years) or evidence of minimum vascular disease (e.g. background retinopathy).
Class F	Renal disease.
Class R	Proliferative retinopathy.
Class RF	Renal disease and proliferative retinopathy.
Class H	Arteriosclerotic heart disease.
Class T	Pregnancy after renal transplantation.

[1] White P. Pregnancy and diabetes. Medical Aspects. Med Clin North Amer 49:1015-1024, 1965.

Appendix II

Antenatal Diabetic Coding form

ANTENATAL DIABETIC CODING

MONM ____ MNO ____

BBNM ____ BNO ____

PART I

STUD NO | REF MD | DEL DT | SEX | BWT

GLUSCR | SCRDT (Y.M.D) | GTT AC | 1H | 2H | 3H

GTT DT (Y.M.D) | DIAG | DIAG DT (Y.M.D) | CH | CH DIAG (Y.M.D) | STATUS

HT | PRE WT | W/A

PART II

DATE				
VIS NO				
WT				
KCAL	AC	AC	AC	AC
UR GLU				
UR KET				
BG AL				
BG PL				
INSUL				
EDEMA				
BP				
HGAIC				

DATE				
VIS NO				
WT				
KCAL	AC	AC	AC	AC
UR GLU				
UR KET				
BG AL				
BG PL				
INSUL				
EDEMA				
BP				
HGAIC				

SPEC INFO & DATE: _____

Appendix III

Antenal Diabetic Coding Definitions

PART I: Patient identification and diagnosis

Mother's name (MONM)
married, maiden and first 4 letters of first name

Mother's number (MNO)
6 digits, RVH case number

Infant's name (BBNM)
surname if known

Infant number (BBNO)
6 digits, RVH case number

Study number (STUD NO)
4 digits, assigned consecutively during Part I of data collection

Referring doctor (REF MD)
surname of obstetrician who referred pt to clinic

Date of delivery (DEL DT)
6 digits, year-month-day

Sex of infant (SEX)
1 = female
2 = male

Infant's birthweight (BWT)
0 to 9999 grams

Glucose screen result (GLUSCR)
0.1 to 99.9 mmol/L, or 0 to 999 mg/dL before Aug 1985

Date of glucose screen
6 digits, year-month-day

Glucose tolerance test (GTT)
4 values: fasting (AC), 1 hour (1H), 2 hour (2H), 3 hour (3H)
0.1 to 99.9 mmol/L, or 0 to 999 mg/dL before Aug 1985

Date of glucose tolerance test (GTTDT)
6 digits, year-month-day

Diagnosis (DIAG)
1 = impaired gluocse tolerance
2 = class A1
6 = class D
7 = class F

3 = class A2
4 = class B
5 = class C
8 = class H
9 = class R
10 = class T

Date of diagnosis (DIAG DT)
6 digits, year-month-day

Change of diagnosis during pregnancy (CH)
0 = no change
1 = impaired glucose tolerance to class A2
2 = class A1 to A2
3 = class B to D
4 = class C to D
5 = class C to T
6 = class C to R
7 = class D to R
8 = class D to F

Date of change in diagnosis (CH DT)
6 digits, year-month-day

Eligibility status (STATUS)
Included:
0 = all data available
7 = preterm labour
Excluded:
1 = ADC data not available
3 = MOND data not available
4 = diabetic class B, C, D, F, H, R, T
5 = baby not delivered at the RVH
6 = presented to clinic for less than 3 visits or after 36 weeks
8 = Chonic hypertension
9 = maternal, fetal or neontal condition which influences birthweight
10 = twins

Height (HT)
0 to 999 cm, blank if unknown

Pregravid weight (PRE WT)
20.0 to 250.0 kg, or 20.0 to 500.0 lb before November 1987

Race (RC)
1 = white
2 = black
3 = asian
4 = other

Cigarettes (CIG)
number of cigs smoked per day
0 to 100, 999 amount unknown, blank if none

PART II: Measures from weekly visits

Date of ADC visit (DATE)
6 digits, year-month-day

Visit number (VISNO)

number of visits accumulated to date, including index visit

Weight (WT)
20.0 to 250.0 kg, or 20.0 to 500.0 lb before November 1987

Daily energy intake (KCAL)
derived as described in Methods section
1000 to 4000 kcal/day

Accuarcy of daily energy intake (AC)
reflects the adequacy of data used to determine KCAL
1 = good
2 = fair
3 = poor

Carbohydrate (C)
50 to 500 grams of carbohydrate consumed per day

Protein (P)
50 to 500 grams of protein consumed per day

Urine glucose (UR GLU)
summary of frequency and severity of glycosuria from past week; based on record of home
monitoring done 4 times/day
0 = none present
1 = present in small amount, 2-4x
2 = present in moderate amount, 4-8x during week
3 = present in large amount, every day 2x or more
9 = unknown if present or not

Urine ketones (UR KET)
summary of frequency and severity of ketonuria from past week; based on patients record
of home monitoring done 4 times/day
0 = none present
1 = present in small amount, 2-4x
2 = present in moderate amount, 4-8x during week
3 = present in large amount, every day 2x or more
9 = unknown if present or not

Blood glucose, fasting (BGAC)
measured at clinic before breakfast
0.1 to 99.9 mmol/L, blank if not measured

Blood glucose, post-prandial (BGPC)
measured at clinic 1hour after breakfast
0.1 to 99.9 mmol/L, blank if not measured

Insulin dosage (INSUL)
total units of insulin taken prior to clinic visit
1 to 300 units, blank if not taken

Edema (EDEMA)
as assessed by nurse at clinic visit
0 = absent
1 = trace
2 = small amount, (1+)
3 = moderate amount, (2+)
4 = severe amount, (3+)
9 = not recorded

Toxemia (BP)
blood pressure elevated and edema severe
0 = absent
1 = present

Glycosylated hemoglobin (HGAIC)
measured from fasting blood approximately every 4 weeks
0.001 to 9.999

Special information and date
any additional information which may influence interpretation of data

Appendix IV

Maternal and Neonatal Variables

A. Antenatal Diabetic Variables from ADC Chart

Part I of ADC Coding Form
Mother's name
Mother's hospital case number
Baby's hospital case number
Study number
Referring physician
Delivery date
Sex of infant
Birth weight

Glucose screen value
Date of glucose screen
Oral glucose tolerance values
Date of OGTT
Diabetes diagnosis (White's Classification of Diabetes in Pregnancy)
Date of diagnosis
Change of diagnosis
Date of change of diagnosis
Eligibility status

Part II of ADC Coding Form
Mother's height
Mother's prepregnancy weight
Mother's race
Cigarettes smoked per day

Weekly record of:
Date of clinic visit
Maternal weight
Average daily intake of: Energy
Carbohydrate
Protein
Accuracy of dietary intake
Urine glucose
Urine ketones
Fasting plasma glucose (AC)
One hour post-prandial plasma glucose (PC)
Insulin dosage
Presence of edema
Presence of toxemia
Glycosylated hemoglobin

B. Derived Variables from ADC Chart

Average daily energy intake/kg pregravid body weight
Total weight gain at diagnosis of GDM
Total weight gain at delivery
Incremental weight gain from diagnosis to parturition
Body mass index
Mean fasting blood glucose during treatment of GDM
Mean 1 hour post-prandial blood glucose during treatment of GDM
Gestational age at each ADC visit

C. Maternal Variables from MOND	MOND code
Mother's date of birth	MBIRTHD
Hospital of Origin	HOSPORIG
Attending physician	MDPREG
Gravidity	GRAVID
Parity	PARITY
Aborta	ABORTA
Living children	LIVING
Date of last normal menstrual period	LNMP
Abnormalities of previous pregnancies	PREVABN1
	PREVABN2
Previous caesarean section	PREVCS
Interval since previous delivery or abortion	INTERV
Years of schooling	SCHOOL
Cigarettes smoked per day	SMOKING
Alcohol intake during pregnancy	ALCOHOL
Social drugs	SOCDRUGS
Induction of labor and indication	INDUCT
Delivery date	DELIVDAT
~~Induction of labour and indication~~	~~NDUCT--~~
Method of delivery	METHDEL
Indication for caesarean section	CSECT
Genital lacerations and maternal trauma	LACER
Placental weight	PLACWT
Expected date of confinement by early ultrasound	EDCUS
Estimated fetal weight on last ultrasound	LASTEFW
Disorder of amniotic fluid volume	AMNIOVOL
Placental maturity on last ultrasound	USMATUR
Maternal outcome	MOUTCOM
Disorders and maternal diseases	MDIS1
	MDIS2
Dystocia, inertia and other complications	DYSTOC
Hypertensive disorders of pregnancy	HYPERTEN
Albuminuria in pregnancy	HTALBUM

D. Neonatal Variables from MOND

Sex	SEX
Birth weight	BWEIGHT
Birth length	BLENGTH
Birth head circumference	BHEAD
Clinical assessment of gestational age	GESTCLIN
Apgar score at 1 minute	APGAR1
Apgar score at 5 minutes	APGAR2
Duration of manual ventilation	DURVENT
Fractures	FRACT
Paralysis	PARALYS
Respiratory distress syndrome: clinical severity	RDSCLIN
Neonatal outcome	BOUTCOM
Cause of death	DEATHCA
Highest hemoglobin (g %)	HEMOHI
Lowest plasma glucose (mg %)	GLUCLO
Peak indirect bilirubin (mg %)	BILIRUB
Number of umbilical vessels	UMBIL

E. Dervied Variables from MOND

Gestational age by LNMP	GESTLNMP
Gestational age by ultrasound	GESTUS
Gestational age assigned	GESTASS
Gestational age type	GESTASST
Malformation flag	MALFORM$
Systemic infection flag	SYSINF$
Birth weight ratio	BWRATIO
Fetal growth rate by ultrasound	USGROWTH

Appendix V

Variable Summarization

The independent and dependent variables studied are described below

Maternal age was calculated in years by applying the SAS month-day-year function to the maternal birthdate and the date of diagnosis for GDM; categories for maternal age were presented in the descriptive results, however it was used as a continuous variable in the regression analysis.

Parity indicates the number of children born to a woman prior to the index pregnancy; this variable was classified as nulliparous (no previous children), primiparous (one previous child), or multiparous (two or more previous children) for descriptive analysis and was used as a continuous variable in multiple regression.

Smoking data was based on the number of cigarettes smoked per day during pregnancy and was presented as the percentage of the population that smoked, as well as by three categories of the amount of cigarettes smoked; for the purposes of regression analysis a binary variable was created as non-smoker or smoker.

Years of schooling was available for about 80% of the women and was used as a proxy for socioeconomic status; it was presented as an interval variable according to the Quebec school system, that is grade school (0-8 years), high school (9-11 yrs), CEGEP college (12-13 yrs), undergraduate studies at university (14-17 yrs), and post-graduate studies (>17 yrs). In regression analysis is was entered as a continuous variable.

Prepregnancy body mass index (BMI) was calculated with the following equation:

$$BMI = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2}$$

, using prepregnancy weight in kg, and maternal height in m.

Prepregnancy BMI was classified as an interval variable using the IOM (1990) categories of underweight, normal weight, overweight and obese for descriptive analysis, while in

regression analysis BMI was entered as a continuous variable.

Race was obtained from the diabetic clinic chart which indicated race as white, black, asian, or other (usually specified) and was available for 80% of the the subjects. This variable was presented in the descriptive results and was not used in regression analysis.

Information on alcohol and social drug consumption during pregnancy was obtained from the MOND system, which derived the information from a preadmission form completed by the patients prior to labor and delivery. The amount of alcohol is presented in descriptive results, however the amount of cannabis consumed was not reported and so this variable indicated whether or not this drug was consumed.

Diagnosis was classified as either impaired glucose tolerance (one abnormal OGTT value), class A1 diabetes (two abnormal OGTT values and treated by diet alone), or class A2 diabetes (two abnormal OGTT values and treated by insulin and diet). Since some classifications changed during treatment as women were started on insulin, the diagnosis reported in the results is the final diagnosis at the time of delivery.

Gestational age at diagnosis in weeks was calculated by SAS using the gestational age at delivery and the date of diagnosis (the date of the initial evaluation by the endocrinologist, that is the first clinic visit).

The **dietary intake data** is presented as calories of energy and grams of carbohydrate, protein and fat consumed/day for the whole sample and for stratified subsets according to prepregancy BMI and treatment groups. Methods section C.2 describes collection of dietary data. In addition, energy intake was presented as kilocalories/kg of prepregnancy body weight and as distribution from the macronutrients. These variables were used in the descriptive analysis and mean energy intake was also used in the multiple regression analysis.

Mean gestational weight gain in kg was presented as a total gain (maternal weight at delivery less prepregnancy weight), pre-diagnostic weight gain (weight at diagnosis less prepregnancy weight), and post-diagnostic gain (maternal weight at delivery less weight at diagnosis). **The mean rate of weight gain** in kg/wk was determined for the pre-diagnostic period (pre-diagnostic weight gain divided by weeks of gestation at

diagnosis) and for the post-diagnostic period (post-diagnostic weight gain divided by the number of weeks from diagnosis to delivery).

Ketonuria frequency and severity was summarized as described in Methods section C.2 and was used as a ranked variable for the purposes of Spearman correlation analysis ketonuria and weekly weight change. The latter variable was derived by calculating the change in maternal weight from one visit to the next

Data on amniotic fluid volume disorders were derived from MOND and diagnosed by a physician's clinical evaluation or ultrasound examination. **Preterm labour** was described in the diabetic clinic chart, as diagnosed by the perinatalogist. These conditions were analyzed descriptively only.

Gestational length or age (GA) in days was assigned by MOND using either the GA by the last normal mentrual period or by the GA by an early ultrasound; the former GA was used if known, unless it differed from the latter GA by more than 7 days, in which case GA by ultrasound was used. This method of GA estimation utilized at this institution is described by Kramer and coworkers (1988).

Treatment length in weeks was calculated by subtracting the GA (weeks) at diagnosis from the GA (weeks) at delivery.

Mean fasting and postprandial plasma glucose values (mmol/L)were derived from the sum of these respective values during treatment divided by the number of values. These values were used in the descriptive and regression analysis.

All variables related to labor, delivery and infant outcome were obtained from MOND and were analyzed descriptively. Birthweight and birthweight ratio were also used as the continuous dependent variables in multiple regression analyses. Birthweight ratio is derived by MOND using the infant's birthweight divided by the standard birthweight for the infant's gestational age; this method has been described by Usher and McLean (1969).

Appendix VI

Tables 19a to 19l

Table 19a. Multiple regression analysis of potential predictors of birthweight in grams (N=436)

Dependent variable:	Birthweight			Birthweight ratio	
R square:	0.233			0.194	
Parameter [1]	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1681.05	0.0873	980.201	0.4915	0.0046
Gestational age	11.33	0.0002	2.988	--	--
Body mass index	16.73	0.0001	3.805	0.0049	0.0001
Height	6.41	0.0297	2.722	0.0017	0.0610
Parity	31.99	0.0602	16.87	-.0011	0.3643
Smoker	-206.58	0.0001	48.231	-.5409	0.0004
Infant gender	88.64	0.0268	39.25	0.0272	0.0297
Treatment with diet or diet and insulin	51.34	0.3198	51.962	0.0321	0.0448
Mean fasting PG	96.02	0.0166	47.732	0.0266	0.0344
Days of treatment	-1.25	0.0767	0.682	-.0003	0.1303
Rate of weight gain prior to diagnosis	784.80	0.0001	122.644	0.2162	0.0001
Rate of weight gain during treatment	14.80	0.8055	54.679	0.0038	0.8428
Mean daily energy intake	0.017	0.9214	0.148	0.05E4	0.9259

[1] Units for the parameters are:

Gestational age: days
Body mass index: kg/m^2
Height: cm
Age at diagnosis: years
Smoker: no, yes
Infant gender: female, male
Mean fasting PG: mmol/L
Rate of weight gain: kg/wk
Mean energy intake: kcal/d

Table 19b. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.235		0.194	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1564.148	0.0895	944.56	0.4333	0.0043
Gestational age	10.928	0.0002	2.95	—	—
Body mass index	17.087	0.0001	3.73	0.0052	0.0001
Height	6.450	0.0228	2.82	0.0019	0.0343
Smoker	-210.621	0.0001	47.95	-.0569	0.0002
Infant gender	92.237	0.0206	39.69	0.0285	0.0216
Parity (0,1,>1)	31.753	0.0612	16.92	0.0118	0.0248
Mean fasting PG	113.423	0.0017	35.97	0.0330	0.0033
Days of treatment	-0.985	0.1320	0.65	-.0002	0.2445
Rate of weight gain prior to diagnosis	773.559	0.0001	122.36	0.2263	0.0001

[1] units of parameters are same as indicated in footnote 1 Table 19a

Table 19c. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.162		0.127	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1595.399	0.1076	989.31	0.4191	0.0081
Gestational age	10.980	0.0004	3.08	—	—
Body mass index	11.508	0.0024	3.77	0.0036	0.0021
Height (cm)	7.978	0.0069	2.94	0.0024	0.0099
Smoker	-200.068	0.0001	50.10	-.0544	0.0022
Infant gender	102.712	0.0136	41.47	0.0319	0.0137
Parity	13.847	0.4287	17.48	0.0064	0.2356
Mean fasting PG	156.779	0.0001	36.81	0.0452	0.0001
Days of treatment	-1.284	0.0440	0.64	-.0003	0.1597

Table 19d. Regression analysis of "core" variables (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.116		0.087	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1193.132	0 2332	999.39	0.5886	0.0002
Gestational age	11.587	0.0002	3.13	—	—
Body mass index	16.033	0.0001	3.58	0.0051	0.0001
Height	7.762	0.0097	2.99	0.0023	0.0138
Smoker	-211.487	0.0001	51.15	-.0574	0.0003
Infant gender	102.761	0.0158	42.42	0.0319	0.0153

Table 19g. Regression analysis of core plus length of treatment (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.123		0.090	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1055.168	0.2914	998.95	0.5856	0.0002
Gestational age	11.032	0.0005	3.14	—	—
Body mass index	17.176	0.0001	3.62	0.0053	0.0001
Height	8.035	0.0073	2.98	0.0023	0.0117
Smoker	-209.646	0.0001	51.01	-.0570	0.0004
Infant gender	102.000	0.0163	42.29	0.0318	0.0156
Days of treatment	-1.230	0.0568	0.64	-.0003	0.2072

Table 19h. Regression analysis of core with treatment group (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.120		0.099	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1382.619	0.1702	1006.29	0.5763	0.0002
Gestational age	12.184	0.0001	3.15	—	—
Body mass index	14.258	0.0002	3.77	0.0042	0.0004
Height	7.617	0.0111	2.99	0.0022	0.0166
Smoker	-204.97	0.0001	51.27	-.0542	0.0007
Infant gender	8.081	0.0214	42.48	0.0296	0.0243
Treatment included insulin	68.491	0.1415	46.49	0.0338	0.0176

Table 19i. Regression analysis of core with total weight gain (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.210		0.162	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1111.549	0.2406	945.81	0.4750	0.0017
Gestational age	9.766	0.0011	2.98	—	—
Body mass index	23.724	0.0001	3.56	0.0072	0.0001
Height	6.966	0.0142	2.83	0.0021	0.0200
Smoker	-208.329	0.0001	48.41	-.0564	0.0002
Infant gender	103.274	0.0104	40.14	0.0322	0.0109
Total weight gain (kg)	26.932	0.0001	3.76	0.0073	0.0001

Table 19j. Regression analysis of core with pre-diagnostic weight gain (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.216		0.161	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-686.181	0.4679	944.52	0.5155	0.0006
Gestational age	8.727	0.0036	2.98	—	—
Body mass index	23.008	0.0001	3.51	0.0069	0.0001
Height	6.504	0.0216	2.82	0.0019	0.0278
Smoker	-210.988	0.0001	48.22	-.0571	0.0002
Infant gender	97.560	0.0151	39.99	0.0308	0.0150
Weight gain prior to diagnosis (kg)	27.056	0.0001	3.65	0.0070	0.0001

Table 19e. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.205		0.163	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1118.139	0.2385	947.21	0.5654	0.0002
Gestational age	10.850	0.0003	2.98	—	—
Body mass index	21.427	0.0001	3.50	0.0065	0.0001
Height	6.030	0.0352	2.85	0.0017	0.0542
Smoker	-219.023	0.0001	48.52	-.0589	0.0001
Infant gender	93.011	0.0214	40.29	0.0289	0.0216
Rate of weight gain prior to diagnosis (kg/week)	833.186	0.0001	119.37	0.2395	0.0001

Table 19k. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.119		0.096	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1272.162	0.2041	1000.32	0.6144	0.0001
Gestational age	12.063	0.0001	3.15	—	—
Body mass index	14.281	0.0002	3.82	0.0042	0.0004
Height	7.582	0.0115	2.99	0.0022	0.0177
Smoker	-205.627	0.0001	51.30	-.0545	0.0006
Infant gender	98.803	0.0205	42.49	0.0299	0.0228
Insulin dosage	43.153	0.1872	32.67	0.0214	0.0333

Table 19f. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.153		0.121	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-1660.835	0.0926	985.26	0.4359	0.0058
Gestational age	11.378	0.0002	3.07	—	—
Body mass index	10.553	0.0049	3.73	0.0035	0.0027
Height	7.471	0.0111	2.93	0.0022	0.0158
Smoker	-200.398	0.0001	50.19	-.0541	0.0006
Infant gender	104.373	0.0124	41.57	0.0324	0.0122
Mean fasting plasmaglucose	159.400	0.0001	36.77	0.0464	0.0001

Table 19l. Regression analysis of all women (N=436)

Dependent variable:		Birthweight		Birthweight ratio	
R square:		0.169		0.147	
Parameter	Regression coefficient	p value	Standard error	Regression coefficient	p value
Intercept	-2091.283	0.0344	985.30	0.3610	0.0212
Gestational age	12.291	0.0001	3.04	—	—
Body mass index	11.625	0.0012	3.58	0.0036	0.0011
Height	8.447	0.0038	2.90	0.0025	0.0054
Smoker	-194.493	0.0001	49.76	-.0519	0.0008
Infant gender	101.102	0.0145	41.18	0.0314	0.0139
Mean post-prandial plasma glucose	114.546	0.0001	21.93	0.0370	0.0001

Appendix VII

Tables 20a to 20c

Table 20a. Regression analysis of women normal pregravid BMI (n=244) Dependent variable: Infant birthweight

Independent variable	Regression coefficient	p value	Standard error	R square
Intercept	-1943.145	0.1289	1275.071	0.238
Gestational length	8.803	0.0152	3.601	
Body mass index	40.696	0.0049	14.336	
Height	10.877	0.0089	4.123	
Smoker	-196.688	0.0008	57.590	
Infant gender	138.276	0.0034	46.752	
Maternal age	-1.961	0.6898	4.906	
Rate of weight gain prior to diagnosis	705.913	0.0002	183.203	
Fasting plasma glucose	39.066	0.4683	53.783	

Table 20b. Regression analysis of women with Overweight and Obese pregravid BMI (n=140) Dependent variable: Infant birthweight

Independent variable	Regression coefficient	p value	Standard error	R square
model 1				
Intercept	1260.157	0.4890	1816.092	0.259
1. Gestational length	6.988	0.2146	5.603	
2. Body mass index	5.473	0.4761	7.658	
3. Height	-2.035	0.6707	4.776	
4. Smoker	-219.909	0.0247	96.772	
5. Infant gender	-44.171	0.5860	80.903	
6. Maternal age	-6.330	0.4209	7.840	
7. Rate of weight gain prior to diagnosis	710.242	0.0001	180.619	
8. Fasting plasma glucose	204.345	0.0004	56.011	
model 2: "core" model				
1, 2, 3, 4, and 5				0.042
model 3				
Rate of weight gain prior to diagnosis	813.771	.0001	181.644	0.129
model 4				
Fasting plasma glucose	245.954	.0001	57.492	0.118
model 5				
1, 2, 3, 4, 5 plus				
Length of treatment	-2.151	0.0329	0.9978	0.074

Table 20c. Regression analysis of women Obese pregravid BMI (n=96)
Dependent variable: Infant birthweight

Independent variable	Regression coefficient	p value	Standard error	R square
model 1				
Intercept	761.775	.7556	2439.336	0.298
1. Gestational length	11.660	.1315	7.656	
2. Body mass index	9.349	.3772	10.531	
3. Height	-1.642	.7767	5.772	
4. Smoker	-215.036	.0863	123.913	
5. Infant gender	5.887	.9559	106.264	
6. Maternal age	-1.527	.8803	10.109	
7. Rate of weight gain prior to diagnosis	820.253	.0003	215.809	
8. Fasting plasma glucose	264.755	.0011	78.221	
model 2:				
Rate of weight gain prior to diagnosis	889.764	.0001	215.576	0.156
model 3:				
Fasting plasma glucose	275.494	.0008	79.419	0.115