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Medical Nutritional Therapy for Pre-gestational and Gestational Diabetes Mellitus

Lois Jovanovič[1, 2]

1. Keck University Medical School, Los Angeles, California, USA

2. University of Southern California, Santa Barbara 93109, California, USA

Abstract: Pregnancy causes a multitude of metabolic changes within a woman's body in order to provide the proper nutrients to the developing fetus. In women with diabetes type 1, type 2, and GDM (gestational diabetes mellitus) these metabolic perturbations must be treated distinctly and aggressively to optimize fetal development and health. Pre-gestational diabetes (either type 1 or type 2) has the potential to subject the developing fetus to abnormal maternal glucose levels resulting in problems with organogenesis producing congenital abnormalities or spontaneous abortion. Furthermore, gestational diabetes mellitus presents after organogenesis in the second part of pregnancy, therefore the major risk for the fetus is macrosomia. Although the goal for dietary therapy for each of these disorders is the same which is euglycaemia, the means to achieve it are very different and somewhat controversial. In the case of gestational diabetes, the main stay of therapy is medical nutritional therapy whereas in insulin requiring diabetes, dietary therapy is compensated with pre-meal insulin injections. The metabolic changes in normal pregnancy will be presented followed by the general guidelines for pregnancy. Fetal complications associated with inadequate nutrition or metabolic perturbation will be briefly explored, followed by issues and treatment for gestational diabetes mellitus, with emphasis on specific dietary therapies for GDM.

Key words: Glucose control, peak post prandial glucose concentration, macrosomnia, pregnancy, glucose mediated complications of pregnancy.

1. Introduction

Pregnancy causes a multitude of metabolic changes within a woman's body in order to provide the proper nutrients to the developing fetus. In women with diabetes type 1, type 2, and GDM (gestational diabetes mellitus) these metabolic perturbations must be treated distinctly and aggressively to optimize fetal development and health. Pre-gestational diabetes (either type 1 or type 2) has the potential to subject the developing fetus to abnormal maternal glucose levels resulting in problems with organogenesis producing congenital abnormalities or spontaneous abortion. Furthermore, gestational diabetes mellitus presents after organogenesis in the second part of pregnancy, therefore the major risk for the fetus is macrosomia. Although the goal for dietary therapy for each of these disorders is the same which is euglycaemia, the means to achieve it are very different and somewhat controversial. In the case of gestational diabetes, the main stay of therapy is medical nutritional therapy whereas in insulin requiring diabetes, dietary therapy is compensated with pre-meal insulin injections. In this chapter, the metabolic changes in normal pregnancy will be presented followed by the general guidelines for pregnancy. Fetal complications associated with inadequate nutrition or metabolic perturbation will be briefly explored, followed by issues and treatment for gestational diabetes mellitus, with emphasis on specific dietary therapies for GDM.

Corresponding author: Lois Jovanovič, professor, research fields: bioscience and engineering.

2. Metabolic Changes in Normal Pregnancy

During pregnancy, metabolism increases by 15-26% to support both mother and developing fetus [1]. Early pregnancy is characterized by normal glucose tolerance, normal hepatic gluconeogenesis, and normal or improved insulin sensitivity [1-5]. As pregnancy progresses, carbohydrate metabolism

becomes altered due to an increase in insulin secretion and decreased insulin sensitivity. Thus, some insulin resistance occurs, by late pregnancy overall insulin action is decreased 50% to 70% as compared to a non-pregnant woman [5].

Lipid metabolism is also altered in hepatic and adipose tissue. Early pregnancy hormones, estrogen, progesterone, and insulin promote the storage of lipids within maternal tissues. Therefore, in early pregnancy, initially there is a decrease in serum triacylglycerol, fatty acids, cholesterol, lipoproteins, and phospholipids. However, as estrogen and insulin resistance impacts the mother, lipolysis and hypertriglyceridemia ensues [5]. For example at week 12, estrogen causes cholesterol, specifically HDL (high density lipoprotein), to be utilized as a major metabolic fuel for the placenta throughout the remaining weeks of pregnancy, thus serum concentrations increase. Furthermore, VLDL (very low-density lipoprotein) is altered in the second and third trimesters due to a change in adipose and hepatic enzyme activity, specifically the decrease of LPL (lipoprotein lipase). Notably, when maternal glucose levels decrease as can be seen during the fasting state, hepatic LPL activity increases allowing the mobilization of lipids and ketones for fetal nutrition [5].

Human chorionic gonadotropin, prolactin, and glucagon also contribute by stimulating lipolysis in late pregnancy. This serves to preferentially send glucose and protein to the fetus, while the maternal tissues rely more on fatty acid oxidation and ketogenesis to meet their energy requirement. Finally, during the third trimester a change in hepatic gluconeogenesis can be seen. Due to a 10-15 mg/dL decrease in basal rate of glucose and an insulin concentration of two times the concentration seen in a non-pregnant woman, the liver must compensate by secreting 16-30% more glucose to meet the energy needs of both the mother and fetus [3, 6-7]. Assel et al. found that the maternal hepatic glucose production is dependent upon maternal body weight in a linear fashion. Late pregnancy also is characterized by a rise in the carbohydrate contribution to the overall oxidative metabolism as an energy source [5].

In normal pregnancy, metabolic changes occur to shunt nutrients from the mother to the fetus, allowing for optimal development and growth, however as we explore the following sections of this chapter it will become apparent that alteration based on input and dysfunction can alter the body's natural plan and cause both distress to the mother and fetus.

3. General Nutritional Guidelines for Pregnancy

Normal pregnancy nutritional guidelines focus on several dietary elements. Major topics include: caloric intake, macronutrient proportion, vitamins and minerals, and alcohol consumption. The energy requirements of the fetus must be met to ensure proper development and provide for postpartum lactation without causing excessive maternal weight gain. The energy standard to support a pregnancy has been debated heavily and will be explored in the GDM nutritional therapy section below. The American College of Obstetricians and Gynecologists advocates several basic concepts for a balanced diet for pregnant women. They suggest eating 3 to 4 servings of fruits and vegetables, 9 servings of whole grains for energy, 3 servings of dairy for calcium and 3 servings of meat to reach daily protein requirements. Vitamin supplementation to achieve daily nutrients, as an adjunct to a healthy diet, is encouraged when recommended by the woman's physician. Certain foods should be avoided in pregnancy due to fetal developmental harm. These include: deli meat, certain preparations of smoked fish, soft cheeses, unpasteurized milk, refrigerated pate, raw meat, and raw eggs, which have been associated with bacterial infections such as *Salmonella*, *Listeria*, and *E. coli.*, *T. gondii*, the protozoan that causes Toxoplasmosis, has also been found as contaminant in unwashed

vegetables and raw meat. Fish containing mercury and raw shellfish should be avoided. Caffeine has been associated with miscarriage, premature birth, low birth weight, and withdrawal symptoms in the neonate when consumed in large amounts in pregnancy. However, other studies have implicated caffeine intake in modest levels to be non-detrimental in pregnancy. Until further studies can evaluate caffeine's effects, it is recommended to be avoided altogether [8, 9]. Alcohol should not be used in any amount during pregnancy. *In utero* exposure has been linked to developmental disorders such as fetal alcohol syndrome. Also, alcohol should be avoided postpartum while breast feeding [10].

4. Gestational Diabetes Mellitus

As discussed in the previous section on metabolic changes in pregnancy, the non-diabetic women undergo drastic and dynamic metabolic changes to provide glucose as the preferential energy source to the developing fetus. Although, the pathophysiological mechanism behind GDM remains unknown, some current theories include a predisposition to future type 2 diabetes triggered by the changes in metabolism that normally accompany pregnancy, or an increased response by the woman's body to normal metabolic changes of pregnancy. GDM has been defined as "glucose intolerance of variable severity with onset or first recognized during pregnancy" [11]. It is important to note that GDM does not cause a malfunction in insulin secretion or improper proinsulin or glucagon activity: insulin resistance remains the prominent characteristic [12]. In the United States, GDM affects 2% to 14% of the pregnant population per year depending on the ethnicity of the population studied [13, 14]. A woman who is most likely to be affected by GDM is one who is obese, > 25 years of age, has a family history of diabetes especially in first degree relatives, has a past medical history for glucose intolerance or metabolism problems and/or miscarriages or other obstetric problems. Additionally, Latino, African, Native American, South or East Asian, and Pacific Islanders are at a higher risk for developing GDM [15]. The Santa Barbara County Health Care Services Program Study [16] found that women who meet several of these criteria, at the greatest risk, should be tested as early as feasible, while those with average risk should be tested at 24 to 28 weeks gestation. However, GDM can easily appear in low risk women, therefore universal screening would be ideal.

5. Screening Methods for GDM

The screening methods for GDM are very controversial. The two criteria sets endorsed by the World Health Organization or the US National Diabetes Data Group are each distinct and are primarily based on statistical standard deviations without regarding the level of clinical outcome achieved. An attempt to set international standards and identify those at risk for developing GDM is currently underway in a five-year, prospective, observational and multi-center study, the Hyperglycemia and Adverse Pregnancy Outcomes Study. It involves 25,000 women in 10 countries and specifically will look at the clinical outcomes with respect to caesarian delivery, fetal hyperinsulinemia, macrosomia, and neonatal morbidity in correlation to maternal glycemic levels [17].

6. Fetal Complications of Maternal Hyperglycemia

Uncontrolled hyperglycemia primarily affects fetal growth on both extremes of the normal growth curve. In those diabetic mothers that have advanced vascular disease, fetal growth deceleration may occur due to placental insufficiency. Fetal growth deceleration is defined as those in lower 5th percentile on a growth curve adjusted for gestational age [18, 19]. Macrosomia defined as an absolute birth weight of greater than 4,000 gnnor greater than the 90th percentile (adjusted for gender, ethnicity and

gestational age). Caesarian sections often must be performed when the baby is at term to reduce the risk of birth trauma such as Erb's palsy or Klumpke's paralysis [20]. A caesarian section also adds risk to the mother's health. As explained by the Pederson hypothesis [21], the effects of an intrauterine environment of hyperglycemia and hyperinsulinemia include: hypoglycemia, organ developmental problems (especially gastrointestinal), erythrocytosis, iron redistribution, Calcium and Magnesium deficiencies, respiratory problems (Respiratory Distress syndrome), cardiac problems (intraventricular hypertrophy and cardiomyopathy or heart failure), hyperbilirubinemia and neurological sequelae.

A multitude of metabolic problems occur that not only affect the immediate future of the neonate, but as these children mature they have a predisposition of future metabolic problems, such as type 2 diabetes and metabolic syndrome [22, 23]. Subsequently, this pattern of metabolic disease takes a cyclic course affecting future generations.

7. Does Treatment of GDM Make a Difference in Pregnancy Outcome?

In June of 2005, Crowther and colleagues published the results of a 10-year multi-center randomized clinical trial in Australia and the United Kingdom called the ACHOIS (Australian Carbohydrate Intolerance Study) in pregnant women. The purpose of the ACHOIS was to determine whether medical nutritional therapy, glucose monitoring, and insulin therapy was superior to routine prenatal care with regard to reducing the risk of perinatal complications and postpartum maternal health status. A total of 1,000 women participated in this trial, 490 in the intervention group, and 510 in the routine care group with eligibility based upon the presence of one or more risk factors for GDM, or a positive 50 g GCT (Glucose Challenge Test) who did not have an indication of pre-gestational diabetes, history of GDM, or an active chronic disease. The WHO criteria were used to identify those with GDM, and women with severe glucose impairments were excluded. Therapies provided to the women in the interventional group consisted of dietary counseling with consideration to pre-pregnancy weight, activity level, normal dietary intake, and weight gain. Women were asked to self-monitor their glucose levels four times a day and proceed with insulin therapy dosage adjustments based upon those levels. Women in the routine care group received care from blinded clinicians as to the status of the previously performed OGTT (Oral Glucose Tolerance Test). However, if the clinician felt the patient was experiencing glucose intolerance, assessment and treatment could be instituted at his or her discretion. Otherwise, prenatal care that was specific to the center visited was given. Primary outcomes included one or more perinatal complications defined as death, shoulder dystocia, bone fracture, and nerve palsy. Admission to the neonatal intensive care unit and jaundice that required phototherapy was also assessed. Secondary outcomes included a consideration of the primary outcome, gestational age at delivery, overall birth weight, and birth weight adjusted for gestational age, and the presence of macrosomia or fetal decelerated growth. Maternal outcomes were assessed on the basis of general and mental health including depression, anxiety, gestational age at birth, mode of birth, weight gain during pregnancy, hospital admissions and prenatal visits, and common complications; such as pregnancy induced hypertension.

The ACHOIS study established several significant results both in the neonatal and maternal outcomes. The rate of serious adverse perinatal outcomes was significantly different between the interventional and routine care groups at 1% versus 4% respectively ($p < 0.01$). This rate established the number needed to treat at 34 to reduce the incidence of perinatal complication. Newborns in the interventional group were admitted to the neonatal intensive care units more often, at a rate of 71% versus 61% admission rate in the routine

group ($p < 0.01$). No significant difference was seen when considering the length of stay in the NICU (neonatal intensive care unit) or use of phototherapy due to jaundice. Thirty nine percent of interventional group mothers were induced into labor versus 29% in the routine care group ($p < 0.001$). However, rates and reason for caesarian sections were similar between the groups [24].

With regard to the secondary outcomes, the interventional group neonates had significantly lower mean birth weights ($p < 0.01$) and were born earlier presumably due to higher labor induction rates. However, when adjusting for gestational age with respect to birth weight there were significantly fewer neonates born to interventional mothers that qualified in the large for gestational age category. Additionally, macrosomia occurred significantly less often, but the rate of infants in the small for gestational age group did not differ between the interventional and routine care groups. Maternal outcomes regarding maternal perception at 3 months postpartum of health showed an improved quality of life in the interventional mothers specifically with a reduction in the incidence depression, 8% versus 17% as measured by the Edinburgh Postnatal Depression Scale [24].

The ACHOIS study clearly shows the benefits of using a multi-faceted approach toward managing GDM to the neonate and the mother. Not only does it advocate dietary and insulin therapies, but when one considers the population chosen and the method of randomization, it supports the use of universal screening. Based on the study design, the interventional group would be equivalent to universal screening practices and the routine group would represent those in which GDM screening is not routine. Therefore, by applying the results of the study in the women receiving routine care, only 34 women would need to be treated with interventional therapies to produce one improved neonatal outcome [24]. Given the severity of an adverse neonatal outcome, this finding would support expanding the GDM screening population to include women who would routinely not be screened for GDM.

8. GDM and Nutritional Therapy

As demonstrated above, management of GDM is multifaceted. Insulin therapy, exercise, and diet are all vital components toward reducing the incidence of maternal hyperglycemia and ultimately fetal complications. The remainder of this chapter will focus on GDM nutritional therapy. There is not currently a universally accepted medical nutritional therapy for the treatment of GDM. The American Dietetic Association advocates the standard medical nutritional therapy for a GDM mother to be the standard therapy advocated in non-pregnant adults with the carbohydrate content standard being < 60% carbohydrate per meal. However, when these standards were followed an increase in insulin therapy was seen in more than 50% of the GDM women [25]. Additional studies have supported lower carbohydrate percentages. For example, in a study involving obese GDM women, when the percent carbohydrate was restricted to 33%, the infants were all within normal birth weight ranges and there was no evidence of maternal ketonemia [26].

9. Ketonemia and Ketonuria

Following an overnight fast, 10% to 20% of all pregnant women have ketones in their blood [27]. This fasting ketonemia or “starvation ketonemia” has not been associated to fetal detriment. However, in studies conducted by Rizzo and colleagues, hyperketonemia during pregnancy, which results from maternal diabetes (hyperglycemia) has been implicated to affect the fetus’s intellectual and behavioral development as measured by Bayley Scales of Infant Development, and the Stanford-Binet Intelligence Scale, which were administered at ages 2 and 3, 4 and 5 respectively. Hence, it was suggested that ketonemia would be avoided in all pregnant women [28].

Buchanan and colleagues contrasted the metabolic response in normal pregnant women without GDM, to those who were obese with GDM. He subjected both groups to an overnight fast and then an extended 18 hour total fast. Obese GDM women had a greater decrease in plasma glucose levels and were not more prone to developing ketonemia than the normal pregnant women. This result would support the use of decreasing the frequency of meals in order to achieve lower pre-prandial glucose levels in obese GDM women [29]. In a study of type 1 diabetic women, Jovanovic and co-workers showed that those infants whose mothers had the lowest beta-hydroxybutyrate levels had the largest infants because mothers' postprandial glucose concentrations were higher due to the increased caloric intake prescribed to avoid the ketonemia [30].

10. Caloric Restriction

Caloric restriction in pregnant women with GDM is another aspect of medical nutritional therapy that needs to be addressed. When women who are classified as obese or overweight prior to pregnancy, the amount of weight gain in pregnancy differs from those who are at a normal or underweight prior to pregnancy. The National Academy of Science has recommended that for women greater than 150% of ideal body weight, no more than 15 pounds should be gained with pregnancy. Optimal infant birth weight was achieved when less than 3 kg or no weight was gained in these women [31]. Hypo caloric diets have been explored in women with GDM based upon a 2,400 kcal/day diet. Investigators [32] compared a 2,400 kcal/day diet to a 1,200 kcal/day diet and achieved significant differences in average glucose and fasting insulin levels, but not in fasting or post glucose challenge tests. Those in the 1,200 kcal/day group developed ketonemia and ketonuria, therefore the study was discontinued due to the controversial association of ketones with fetal developmental harm. Subsequently, in another study conducted by the same investigators, within the first week, when compared with the 2,400 kcal/day diet, a 1,600 kcal/day diet improved fasting and mean daily glucose values without the development of ketonemia. Further studies have advocated a 1,500 kcal/day to 1,800 kcal/day diet for obese women with GDM with similar results [33].

The standards for energy requirements for pregnant women with GDM, as supported by the American College of Obstetrics and Gynecology, determine the amount of energy needed to maintain pregnancy based upon the pre-gravid weight. For GDM women, who are 1.5 times their ideal body weight the caloric intake is 12-15 kcal/kg of the current pregnant weight, while those at less than 0.8 of their ideal body weight are to increase their caloric intake to 35-40 kcal/kg current pregnant weight. For those at 0.8 to 1.2 times their ideal body weight, 30 kcal/kg and those at 1.2 to 1.5 times ideal body weight, 24 kcal/kg current pregnant weight is the standard [15]. The "Euglycemic Diet" advocated the lower range of the spectrum set by the American College of Obstetricians and Gynecologists.

11. Carbohydrate Restriction

The Pederson hypothesis attributes fetal macrosomia due to hyperinsulinemia caused by maternal hyperglycemia. Several studies have shown that when maternal glucose levels are well controlled, the incidence of macrosomia, fetopathy, and caesarian sections decreases [21, 34, 36, 37]. Currently there is not a set standard for pre- and post-prandial levels in GDM women. Optimally, the therapeutic target of glucose levels in women with GDM would be the same as those who are pregnant without diabetes. Normoglycemia in the pregnant, non-diabetic, non-obese woman was demonstrated in studies conducted in 2001, by Paretti and colleagues. In this study, the postprandial mean glucose during the 3rd trimester did not exceed 105.2 mg/dL (5.8 ± 0.27 mmol/L). At 28 weeks gestation the l daily mean glucose levels was (71.9 ± 5.7 mg/dL) and at 38 weeks it increased to (78.3 ± 5.4 mg/dL), which would

coincide with the normal insulin intolerance increase respectively. Ref. [35] also accessed the clinical outcome of these pregnancies based on fetal growth. They found that 1 hour postprandial glucose levels at 28 weeks through the third trimester had a positive correlation to fetal abdominal growth. Furthermore, the results are supportive in attributing the postprandial 1 hour glucose levels as a predictor of infant birth weight, fetal macrosomia, fetal hyperinsulinemia and fetal abdominal circumference in non-diabetic pregnancies [35]. Therefore, one may consider the level of insulin resistance as a spectrum, in which those with GDM are affected in the same way as non-diabetic pregnant women but to a greater extent. Hence, the levels of glycemia achieved in non-diabetic pregnant women to decrease incidence of fetal complications and growth would be applicable to those with GDM.

Another study to support the importance of postprandial glucose levels is the Diabetes in Early Pregnancy study, which was conducted with type 1 diabetic mothers. When postprandial glucose levels increased there was an increased risk of macrosomia. The threshold for the marked increase was seen when postprandial glucose levels reached 120 mg/dL [36]. Thus, a dietary therapy, "The Euglycemic Diet" was developed on the basis of this study.

The Euglycemic Diet takes into account the metabolic changes that occur within the pregnant woman as she goes throughout her day. In the morning a surge of cortisol is seen ("The Dawn Phenomenon"), which causes the release of glucose from stored sources and hepatic gluconeogenesis, thus the blood glucose is higher to begin with. Therefore, a decreased amount of carbohydrate is needed in the breakfast meal. A small study (n = 14), was conducted with GDM women who were greater than 130% of their ideal body weight at 32-36 weeks'gestation. The goal was to achieve a postprandial of 120 mg/dL at 1 hour. None of the patients were on an insulin regimen and a caloric restriction of 24 kcal/kg/day was established. Patients kept a diary of glucose levels four times a day and food intake. The carbohydrate parameters of the diet were as follows: 12.5% of the total daily carbohydrate at breakfast, 28% at lunch and dinner, with the remainder in three snacks disturbed throughout the day. The postprandial glucoses recorded by the women correlated to the carbohydrate intake.

From this study, the author has adapted this diet to achieve optimal control of glycemic levels in her patients. Most GDM women are very compliant and want to do what is necessary to have a healthy baby. By having patients take an active role in their medical care, they can significantly reduce their risk for fetal macrosomia. In a study conducted by Ref. [37] when patients monitored their pre- and post-prandial glucose levels, the risk of fetal macrosomia decreased from 42% to 12%. Additionally, these patients also had lower hemoglobin A_{1c} levels, therefore supporting that they maintained lower glycemic levels. Hemoglobin A_{1c} is an effective clinical tool for accessing glycemic control and can be performed every 2 weeks to chart management because the turnover rate of the red blood cells during pregnancy is only 90 days as compared with 120 days in the non-pregnant state. Thus a significant improvement in glucose control is manifest by a significantly improved Hemoglobin A_{1c} level although the steady state has not been achieved until after six weeks.

Patients monitor their pre- and post-prandial glucose levels and only proceed with a meal when their pre-prandial glucose levels are 90 mg/dL or less, otherwise insulin is initiated. A pre-prandial glucose of 90 mg/dL and a postprandial of 120 mg/dL may seem controversial or strict, however given the risk of macrosomia and the positive outcomes that have been obtained clinically the authors of this chapter advocate these glycemic goals for medical nutritional therapy [38].

It is imperative that patients learn which foods have high carbohydrate content, so educational lessons and

nutritional food label reading are essential for the success of any therapy that is instituted. A laundry list of high carbohydrate foods is recommended to give patients in order to remind them what needs to be portioned. For example, the "Big 5" is potatoes, rice, pasta, bread, tortillas, and cereal. By teaching patients to adhere to a Euglycemic Diet, not only are they able to control their glucose levels effectively, but also they are able to modify their diet postpartum facilitating weight loss. A simple teaching tool is used in Santa Barbara County with pictures of the foods to avoid. The one page handout identifies the foods to avoid, foods to eat with caution and foods that may be eaten that minimally impact on the postprandial glucose concentrations and thus can be eaten liberally. Ideally, a breakfast of less than 33% of the daily carbohydrate intake, lunch at 45%, and a dinner at 55% are suggested to maintain a postprandial glucose level of 120 mg/dL [39].

12. Role of Fats in GDM Therapy

Fat content in the ADA's (American Diabetes Association's) diet consists of less than 25% of the total caloric intake, whereas the Euglycemic Diet is composed of 40% of the total daily caloric intake. The role of saturated and monounsaturated fats in GDM women is different with respect to the uptake of glucose postprandially. In a study comparing these two types of fats, one hour postprandial glucose levels are approximately equal, however, the duration of the elevated glucose levels differs. In GDM women who consumed monounsaturated fat, the glucose levels remained elevated longer and thus insulin dosage had to be adjusted to counteract the maintained elevated glycemia. Conversely, meals consumed containing saturated fat, had a shorter duration of elevated glucose levels, making them preferential with regard to glycemic control of postprandial glucose levels. Furthermore, lower postprandial durations decrease the risk of macrosomia and the need for increased insulin doses [40]. The advocating of saturated fats over monounsaturated fats is understandably controversial due to the correlation that has been made with saturated fats and heart disease in non-pregnant individuals. Further studies are needed to answer whether eating a higher proportion of saturated fat during medical dietary therapy for GDM at approximately gestation weeks 24 to 40, is a significant time period to have adverse long-term effects on the mother versus the benefit of controlling postprandial glucose level duration, which decreases the risk of fetal complication.

13. Role of Protein

Protein Content in the ADA diet and Euglycemic Diet makes up 20% of the total daily caloric intake. Increased satiety has also been correlated with meals that are high in protein content [41, 42]. Thus, this aspect could help morbidly obese patients manage their overall caloric intake especially when moderate caloric restriction therapy is being used. Low carbohydrate/high protein diets in normal pregnant women have been explored notably in the Motherwell studies running from 1938 to 1977. The Motherwell studies suggested a link between increased protein content and low birth weight [43]. Recent studies have expanded the initial Motherwell Studies by looking at the offspring of these studies as adults. It has been hypothesized that increased protein intake can stimulate maternal cortisol production and expose the fetus to high levels of cortisol which may facilitate life long hyper-secretion of cortisol. Herrick [44] and colleagues found a correlation to increased plasma cortisol levels consequently causing hypertension in the adult Motherwell offspring. However, they postulated that the type of protein consumed and the type of carbohydrate paired with it may factor into the physiologic effects seen. Co-factors needed for protein metabolism such as folate and Vitamin B6, may be excluded when certain types of carbohydrate are avoided, such as bread and potatoes and green leafy vegetables, as was done in the Motherwell studies. "In

mothers with a limited capacity to synthesize nonessential amino acids, maternal amino acid oxidation could impair fetal growth as a result of reduced availability of nonessential amino acids." [44] Therefore, the physiologic effect of low birth weight on the fetus would be caused multi-factorially and not just due to high protein consumption. Additional studies will be necessary to determine the role of high protein diets in pregnant women and specifically, in women with GDM.

14. Conclusions

Gestational diabetes is a period of glucose intolerance that manifests at the beginning of the third trimester. Metabolic changes in the normal pregnant women also have a degree of insulin resistance as to shunt glucose preferentially to the fetus, but not to the same degree as GDM women do. GDM causes hyperglycemia and hyperinsulinemia in both mother and fetus via the Pederson Hypothesis. These increased glucose and insulin levels manifest a multitude of fetal and maternal complications, the most prevalent being macrosomia. Other complications include hypoglycemia, erythrocytosis, hypocalcemia and hypomagnesia, hyperbilirubinema, iron redistribution, and neurological effects stemming from these metabolic imbalances. The management of gestational diabetes mellitus is based upon the synergistic effects of medical nutritional therapy, exercise, and an insulin regimen when necessary. Poor gestational metabolic management can be directly linked to the level of neurological functioning of the child and these children are more prone to developing metabolic syndromes such as type 2 diabetes. This would affect generations to come as well. Therefore, the identification and treatment of GDM is crucial.

Screening tests using at-risk formulations and oral glucose tolerance tests remain a point of controversy. Universal screening would be optimal to identify those with GDM. The ACHOIS study clearly showed the benefit of expanding screening and providing medical nutritional therapy, glucose monitoring, and insulin therapy to those in the interventional group as compared to those who received routine medical care. The interventional group significantly had decreased perinatal complications, was lower for gestational age, had lower birth weight, and decreased incidences of macrosomia. Maternal post-partum depression rates were also lower in the interventional group. This study establishes the importance of medical nutritional therapy.

Multiple studies have correlated fetal complications such as macrosomia to 1-hour postprandial glucose levels. By restricting carbohydrate concentration in the Euglycemic Diet and modifying the caloric intake based on pre-gravid weight, success has been achieved in reducing large for gestational age and macrosomic infants. The Euglycemic Diet targets a pre-prandial glucose of 90 mg/dL or less and a 1 hour postprandial of 120 mg/dL. Optimal glucose levels have been heavily debated and there is not currently a universal standard. However, research has shown that normal pregnant women in the 3rd trimester have pre-prandial levels of (71.9 ± 5.7 mg/dL) at 28 weeks and (78.3 ± 5.4 mg/dL) at 38 weeks. In this study, the postprandial mean glucose during the 3rd trimester did not exceed 105.2 mg/dL. This would support advocating lower standards of ≤ 90 mg/dL pre-prandially and 120 mg/dL postprandially to correlate with what fetuses of mothers without GDM are exposed to *in utero*.

Hypocaloric diets have been explored and currently the Euglycemic Diet and the American College of Obstetricians and Gynecologists advocate consideration of the mother's pre-gravid weight when considering the caloric needs per kg/day. The presence of maternal Ketonemia and ketonuria is controversial with respect to fetal development, and the mechanisms and outcomes associated with ketonemia resulting from uncontrolled glucose levels and starvation may be different with respect to detriment to the fetus. Fat content also remains controversial although studies have shown that meals with saturated fat as compared

to monounsaturated fat result in the same hour postprandial glucose level, but the duration of the level is shorter facilitating lower insulin dosages. High protein/low carbohydrate diets are also controversial and in normal pregnant women have been correlated to lower birth weights and adult offspring increased cortisol levels. However, satiety is also important and protein malnutrition should be avoided in pregnancy. More research is necessary to determine the effect of these macromolecules on normal pregnant individuals and those with GDM.

Overall, medical nutritional therapy is one of the staples of GDM management. Women with GDM are very compliant and most are willing to make dietary changes in their lives for the benefit of their baby. The successful triad of medical nutritional therapy, exercise, and insulin therapy for GDM is essential to achieving, not only healthy babies, but affects generations to come as metabolic perturbations and disease is reduced in the offspring [45-48].

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