

Nutrition During Pregnancy and the Effect of Carbohydrates on the Offspring's Metabolic Profile: In Search of the "Perfect Maternal Diet"

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Abstract: Fetal growth and development is primarily dependent upon the nutritional, hormonal and metabolic environment provided by the mother. A wartime famine study in Holland first showed that a low food intake reduces the glucose offered to the fetus and thus produces smaller size infants at birth. Maternal glucose regulation is however affected by numerous factors including physiological changes of pregnancy (e.g. insulin resistance [IR]), pathological conditions (e.g. gestational diabetes mellitus) and maternal nutrition. Maternal glucose is substantially influenced by the type of carbohydrates in the diet through its direct effect on glycemia. The rate at which each carbohydrate raises blood glucose levels after ingestion, can be measured *via* the dietary glycemic index (GI). Carbohydrate type and the GI of the diet enhance or inhibit abnormal hyperglycemia during pregnancy caused by either pathological conditions or the inability of the mother to cope with the physiological IR of pregnancy. In turn, maternal gestational hyperglycemia may be involved in the pathogenesis of IR, impaired glucose tolerance, type 2 diabetes mellitus, the Metabolic Syndrome and subsequent cardiovascular diseases in adult offspring. A low GI maternal diet has been associated with measurable benefits to the offspring. These include a positive effect on altering maternal blood glucose production, insulinemia and reduced adiposity as well as fetal and placental insulin and glucose regulation, fetal growth, birth weight and offspring adiposity. We review the possible links between dietary carbohydrate in health during pregnancy and the effect of maternal carbohydrate ingestion on programming the offspring's metabolic profile.

Keywords: Pregnancy, nutrition, carbohydrates, metabolic profile, glycemic index.

INTRODUCTION

Over-nutrition, under-nutrition or unbalanced nutrition is considered a major cause of ill-health worldwide. The prevalence of overweight is high among children in most developed countries [1]. This increase in type 2 diabetes mellitus (DM) and the metabolic syndrome (MetS) in children possibly implies a combination of factors, the majority of which are related to nutrition during the life cycle [2]. However, whether and to what extent early fetal diet influences the achievement of long-term health requires more investigation.

The biological importance of maternal nutrition is well-established. Not only is it the sole way for the fetus to receive the required nutrients but it also affects the maternal metabolic adjustment capacity to the hormones secreted by the placenta that affect the metabolism of all nutrients.

Nutrition during early development is associated with the offspring's growth, organ development, body composition and body functions. It also exerts long-term effects on

health, morbidity and mortality risks in adulthood, as well as on the development of neural functions and behavior, a phenomenon called 'metabolic programming' [3].

The capacity of the offspring to respond to environmental information during early development was first suggested by the "Thrifty phenotype" hypothesis [4], further indicating that these early-life metabolic adaptations, promote the animal's survival capability [5]. An increased susceptibility of the offspring to chronic diseases including obesity and DM in later life has been described in sub-optimal fetal environments (i.e. over-nutrition or malnutrition) in both humans and animal models [4, 6-8].

The response of the fetus to these insults in the environment during the prenatal period has short-term survival advantages, but may lead to long-term disadvantages. This is because it is associated with increased susceptibility of the offspring to cardiovascular disease, hypertension, type 2 DM and obesity [9]. Indeed, particular growth patterns in early life implicate early-life nutrition as the underlying mechanism for human diseases in adulthood [7, 10, 11]. Insulin resistance (IR), impaired glucose tolerance (IGT) [12-14], type 2 DM and MetS, as well as subsequent cardiovascular diseases in the adult offspring, can be induced from fetal and/or early postnatal hyperglycemia or hyperinsulinism (and also hyperleptinism) as a result of maternal

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gestational hyperglycemia and/or early postnatal overfeeding [12, 15-17].

The composition of the diet during pregnancy also modifies certain maternal risk factors (e.g. IGT, IR, hyperlipidemia etc) and may decrease the risk of developing gestational DM (GDM) [17]. It may also inhibit early metabolic changes in the offspring, associated with abnormal leptin and insulin levels [18].

Some consider the diet's glycemic index (GI) as an independent factor that can cause obesity and increase the risks of DM and heart disease in animals and humans [19-22]. The GI describes the way food, a meal, or a diet affects blood glucose levels during the postprandial period. The effect of the pre- and post-natal dietary profile, as measured by the GI, on the offspring's health has not been thoroughly investigated.

In this article we review the evidence linking periconceptional, pregnancy and lactating diet, in terms of dietary carbohydrate, and the metabolic effects on the offspring's health.

MATERNAL NUTRITION AND OFFSPRING HEALTH

There are different means of achieving fetal malnutrition. The most well-established are 2 models of maternal malnutrition (protein and caloric restriction) and 1 model of maternal over-nutrition (fat and/or sucrose over-nutrition). These maternal dietary models, which are typical of the Western diet, lead to a disturbed fetal nutritional environment [23]. This in turn has been linked to a disturbed metabolic profile, such as IR and glucose intolerance, in the adult offspring [24].

A possible mechanism predisposing to IR, glucose intolerance and DM in adult offspring occurs in the presence of repeated maternal hypoglycemia. This leads to subsequent inhibition of normal endocrine pancreas development and abnormal β -cell mass and β -cell dysfunction at birth [24]. There is further evidence suggesting that the particular phenotype of IR and glucose intolerance is "predominant" enough to be transmitted to a second generation without any further environmental modification [23].

Periconceptional and pregnancy nutrition is important in offspring developmental and functional adverse health offspring outcomes. There is evidence suggesting that maternal undernutrition during the periconceptional period and pregnancy results in altered fetal hypothalamic-pituitary-adrenal axis (HPAA) development and function through increased concentrations of active glucocorticoids in utero and offspring altered expression of glucocorticoid receptors, lower fetal capacity to modulate glucose transport into the muscle (increased expression of glucose transporter type 4 [GLUT4]), increased adiposity, dysfunctional cardiovascular regulation, increased rate of premature birth, altered fetal pancreatic function and insulin signaling through dysfunctional pancreatic β -cell development (reduced β -cell proliferation, islet size, and islet vascularization) and dysfunctional amino acid metabolism [25, 26]. The postnatal consequences of these changes however have not been thoroughly investigated.

Besides periconceptional undernutrition, a developmental modification at any stage can lead to adverse outcomes. A mismatched pre- and post-natal nutrient environment induces a defective cardiovascular function in adult offspring [27, 28].

The developmental stages are important for the fate of the offspring. Nutrition during pregnancy and lactation is of particular importance, as supported by animal experiments. In a striking example, a low fat diet during pregnancy and lactation was successful in protecting from metabolic disturbances in the offspring of obese mice with type 2 DM [29]. The offspring's benefits were reduced hyperphagia, increased leanness, normal insulin sensitivity and glycemia.

To what extent pre and periconceptional maternal dietary status affects the health of the mother and the offspring remains to be elucidated. The pre-pregnancy body mass index (BMI) has been argued to be of greater importance than maternal nutrition per se in developing GDM [30]. Indeed, maternal obesity is a risk factor for the development of maternal GDM and strongly predisposes the offspring to obesity, glucose intolerance and IR in successive generations [31]. Nevertheless, GDM is only 1 of the 3 described models, along with protein restriction and caloric restriction, of a fetal environment leading to disturbed fetal development and offspring metabolic profile [23].

A prospective experiment on rats made a considerable effort to clarify the effect of issues surrounding gestational and lactating nutrition on the offspring's eating behavior, adiposity, circulating glucose and insulin levels, triglyceride and cholesterol concentrations from birth to adolescence [28]. A maternal "junk-food diet" (i.e. rich in fat, sugar and salt) produces rat offspring with increased adiposity, raised circulating glucose, insulin, triglyceride and cholesterol by the end of adolescence in comparison with the offspring of mothers feeding on a balanced chow diet during pregnancy and lactation. The effects are intensified when one considers that both groups of offspring were given free access to junk-food from weaning onwards [28]. The junk-food diet is characterized by high-fat content and high GI and resembles the typical Western diet. These experiments render the carbohydrate quality an important constituent of the maternal diet.

PREGNANCY GLYCEMIA AND INSULINEMIA

A number of metabolic adaptations occur during pregnancy in order for the mother to provide herself as well as the developing fetus a relatively small increase in food intake. Physiologically, progressive IR and compensatory hyperinsulinemia take place to increase the storage of nutrients in maternal fat. Also, the process of slowing glucose uptake into maternal tissues serves to provide nutrients to the fetus. However, pathologic glucose intolerance may appear in the third trimester, without the presence of DM, if the maternal pancreatic β -cells are not able to compensate for their inherent as well as the physiological IR of pregnancy [32].

The fetal pancreas starts developing early in pregnancy, while by mid-gestation and until late gestation it is capable of gradually producing considerable amounts of insulin [33]. The glucose-stimulated insulin secretion of the fetus is

down-regulated by constant hyperglycemia, but enhanced by pulsatile hyperglycemia [34-37]. Recent cell and molecular studies have similarly supported the notion that chronic hyperglycemia down-regulates both fetal glucose tolerance and insulin sensitivity [38].

Although the fetus is known to have a considerable capacity to metabolically adapt to acute and chronic changes in glucose supply, lower maternal blood glucose levels lead to reduced fetal growth rate and infant birth weight [39, 40] while a continuous high maternal blood glucose supply to the fetus may lead to fetal overgrowth and large for-gestational-age (LGA) infants [41]. Indeed, numerous animal and human studies demonstrated an association between fetal growth and size at birth with maternal 24-h blood glucose levels [40-43].

Offspring born to GDM mothers with fasting and daily hyperglycemia have higher birth-weight and are frequently overweight in adolescence [44]. Compared with offspring of healthy mothers, offspring of type 2 diabetic mothers show decreased insulin sensitivity in adulthood even in the absence of IGT [45].

In Pima Indians - a population characterized by a high prevalence of type 2 DM - the offspring of type 2 diabetic mothers had a 3.7-fold higher risk of DM and a higher BMI than their siblings born before their mother developed DM [46]. This suggests an important role for the glycemia of the intrauterine environment beyond the possible attributable genetic factors.

The impact of both intrauterine hyperglycemia and genetic predisposition to type 2 DM was evaluated in a population of pregnant females with both GDM and type 1 DM [47]. The hyperglycemic intrauterine environment involved in both types of DM was associated with the pathogenesis of type 2 DM and pre-DM in adult offspring of women with both GDM and type 1 DM during pregnancy [47]. To support the above argument, an abnormal 2 h glucose level during an oral glucose tolerance test is present in the offspring of both type 2 diabetic and normal glucose-tolerant mothers previously exposed to mildly increased blood glucose levels in the third trimester [48, 49].

Even in the absence of abnormal fasting or 2 h glucose values, in utero hyperglycemia in children exposed to GDM increases the presence of metabolic markers of IR such as fasting plasma glucose (FPG) > 6.0 mmol/L, high density lipoprotein (HDL)-cholesterol < 1.03 mmol/L, triglycerides (TG) > 1.24 mmol/L, white cells (WC) > 90% for age and gender, and 2 h glucose >7.8 mmol/L in these children [50]. At the cellular level, some findings suggest an impaired pancreatic β -cell mass and/or function, arising from possible defects in pancreatic angiogenesis and innervation, abnormal placental glucocorticoid concentrations or modification of parental imprinting [4]. A positive association between postprandial blood glucose levels and measures of fetal adiposity (1 h postprandial glucose and fetal abdominal circumference) is evident in women with normal glucose challenge tests even when the mean measured maternal postprandial glucose levels do not exceed the thresholds for good glucose control in pregestational diabetic pregnancies [51].

Further to the effect of glucose concentrations in the intrauterine environment, insulin itself may program the development of obesity and diabetes when occurring in elevated concentrations during perinatal life. This may occur due to a general increase of fetal food supply (e.g. in overweight pregnant women) and neonatal overfeeding [52].

CARBOHYDRATES AND GLYCEMIC RESPONSE

The role of maternal glycemia and insulinemia is well-established in terms of offspring development and growth, but the exact effect of dietary carbohydrates on the metabolic profile is not yet completely understood.

Conflicting evidence arises when examining the effect of total carbohydrate intake on insulin sensitivity [53]. In fact, a recent dietary intervention found that after 6 months on a low-carbohydrate and high-fat diet, insulin sensitivity improved among obese individuals [54]. The source and the quality of dietary carbohydrates, however, may differentially affect insulin action and thereby affect the degree of IR.

Observational studies have indeed suggested that fasting insulin concentrations are lower among individuals reporting higher dietary fiber [55-57] or whole-grain intakes [58, 59] after adjustment for other lifestyle and also dietary factors. Furthermore, a number of studies show a beneficial effect on insulin sensitivity with a high consumption of dietary fiber [56] or whole-grain foods [60-63].

The GI is an index measuring the glycemic response to various carbohydrate-containing foods and has been used to qualitatively classify dietary carbohydrates [64], thus providing an insight into the glycemic and insulinemic effect of each type of carbohydrate. The GI is defined as the area under the curve of the glucose responses to a carbohydrate-containing food compared to either a specific glucose dose or a specific amount of white bread [65, 66]. The greater the particle size, the lower the glucose and insulin response. The greater the level of processing and refining, the higher the glucose response of a particular carbohydrate (Table 1).

Table 1. Factors Affecting GI of Foods

• Soluble fiber content
• Amylose content
• Particle size
• Method of preparation

Indeed, low GI-resistant starch and soluble fiber together have an additive effect on glycemic response with soluble fiber having a selectively greater effect on postprandial insulin response. In contrast, resistant starch from high-amylose cornstarch greatly affects glucose reduction [67]. Data from older studies also suggest a relationship between high dietary GI and elevated triglyceride concentrations [68], low HDL cholesterol [69], accumulation of fat in liver (non alcoholic fatty liver disease), high adipose tissue and less lean body mass. Also, lower plasma adiponectin, and severe disruption of islet physiology and architecture have been reported for

animals on high GI diets in comparison to low GI diets [19, 70, 71].

The controversy begins with studies indicating an inverse effect between GI and appetite, energy and food intake. In humans, inclusion of an ingredient containing increased soluble fiber and amylose has been argued to increase subsequent energy intakes despite its reduced glycemic and insulinemic effects [72]. Furthermore, carbohydrates with a high GI (glucose, polycose and sucrose) fed in humans suppress subjective appetite and food intake in the short term, in contrast to those with a low GI (amylose and amylopectin) [73]. Whether these studies indicate a missing link between obesity and GI or interpretation of these intervention studies is confounded by the comparison of differing patient populations (e.g. obese non-diabetic subjects, type 2 diabetic subjects), or the differences in age ranges is inconclusive but they do suggest a need for future studies incorporating information such as the variation of the “second meal effect (SME)”.

The SME represents a meal's ability (carbohydrate content and quality) to diminish the glucose response (reduction of glycemia) to carbohydrates eaten during the following meal. Fermentable carbohydrates (such as fiber and resistant starch) independent on their effect on a food's GI regulate postprandial responses to a second meal by reducing non esterified fatty acid (NEFA) competition for glucose disposal, and increasing colonic fermentation in humans [74]. In accordance with the above evidence, an association of gut microbial metabolism and key factors associated with IR has been provided, whereby the composition of indigestible carbohydrates of the evening meal affect glycemic fluctuations and related metabolic risk variables at the next-day breakfast meal through a mechanism involving colonic fermentation [75].

Regardless of the timing of the meals, the amount of carbohydrate tested and the mixture of carbohydrate with other macronutrients in complex meals are also important determinants of the level of response. The glycaemic load (GL) is a measure developed to account for a complex meal's glycaemic response [76, 77]. It has been argued to provide more accurate reflections of the meal's effect on blood glucose levels than the GI but with questionable validity [78, 79].

Another point to consider is the specific characteristics of the subjects to be tested which are important in determining the level of reduction that can be achieved. Therefore, older, less slim, more glucose intolerant subjects have the capacity for greater improvement in glucose and insulin responses than do young, fit, slim subjects.

METABOLIC PROGRAMMING, CARBOHYDRATES AND GI

Maternal glycemia and insulinemia are 2 modifiable factors that are extremely important for the developing fetus. Protein is an important element of the fetal diet, in terms of the effect on the fetus's metabolic profile [4, 80]. Various experimental studies showed that a high-protein and a low-carbohydrate maternal diet can cause harmful effects, such as raised blood pressure and increased cortisol secretion in response to psychological stress in the offspring [81], outlining

the importance of balance, but also introducing carbohydrates as an essential element in the search for the “optimum” pregnancy diet [82, 83]. This is strengthened by the fact that the preferred fuel for fetal growth and development is glucose, a substrate primarily affected by the amount and type of carbohydrate in the maternal diet. In rats, differences in amniotic fluid concentrations of glucose, uric acid and urea nitrogen respond to differing amounts of carbohydrate in the maternal diet [84]. Few studies on the other hand have explored the type of carbohydrate in response to its glycemic response when studying the fetal origins of disease hypothesis [83, 85].

A few studies have supported the notion that the type of carbohydrate in the diet influences glycosylated hemoglobin and maternal plasma glucose levels as well as fetal glucose levels, fetal growth and infant birth weight [22, 85]. In sheep, increased birth weight offspring with a faster growth rate in early postnatal life are produced with maternal transient high glycemic intakes in the third trimester of pregnancy [86]. Also, high compared with low GI diets during pregnancy were associated with heavier infants who had a higher birth centile, a higher ponderal index and a higher prevalence of large-for-gestational age, all being strong predictors of chronic diseases in later life [22, 85, 87]. In contrast, lighter infants with a 2-fold increased risk of being born small-for-gestational-age were delivered by women on a lower-GI diet [22]. However, the dietary type of carbohydrate was not thoroughly recorded in the lower GI diets group, thus confounding the true effect of the diet's GI on the delivery outcome.

Reductions of insulin sensitivity in women consuming Western diets in late pregnancy may be due to the diet itself. Low GI maternal diets with a high fiber content even as an addition to a typical high fat and high sucrose Western diet may reduce levels of insulin resistance [88], a finding with therapeutic implications for the supplementation of low GI products on a Western-high-GI diet.

In addition to the effect of malnutrition in pregnancy on the metabolic profile of the offspring, a study on rats attempted to provide proof on a novel property of low GI diets on the fetal origins of disease hypothesis. In this study, nutritional recovery of adult offspring exposed to a protein deficiency during intrauterine life was evident when they were lactated with a low GI diet (soybean flour) [89]. This can be considered as a dispute of the original idea that a mismatched pre- and post-natal environment would evoke a disturbed metabolic profile and obesity, but appears positively promising in terms of its therapeutic potential.

CONCLUSIONS

Fetal exposure to maternal diabetes and hyperglycemia may contribute considerably to the worldwide diabetes epidemic. Knowledge of the exact environmental influences that affect the diseases of aging may allow us to find novel ways to increase our life-span and quality [90]. From a clinical point of view, universal screening and therapy for all types of metabolic profile disturbances during pregnancy is recommended. These measures might serve as causal approaches to primary prevention. This may be possible by the acquisition of knowledge of the exact dietary factors that

influence maternal and offspring glucose and insulin metabolism, especially in high-risk populations. This may provide the basis for health interventions targeting individuals who have increased susceptibility to a disturbed metabolism before pregnancy or have already been exposed to a diabetic environment *in utero* [91].

Recent studies have demonstrated that increasing whole grain intake in the population can result in improved glucose metabolism and delay or reduce the risk of developing type 2 DM. Whole grains can thus provide a substantial contribution to the improvement of the maternal diets, particularly those characterized by the model of western nutrition of high GI carbohydrates and high saturated fatty acid content. A number of different whole grain foods and grain fiber sources were beneficial in IR reduction and improvement in glucose tolerance all characterized by a low GI. Replacing low fiber grain foods, such as cornflakes or white bread, with whole grain higher fiber or higher amylose content products will reduce the risk of developing IR and obesity and improve the health of the US population. Form, amount and method of cooking of these foods, as well as the health characteristics, age and gender of the group of subjects studied are all important factors in the effectiveness of the foods in altering these responses [66].

Further to the insulinemic and glycemic effect, a high GI independently causes obesity and increases the risk of diabetes and heart disease in animals. The use of low-GI diets in prevention and treatment of human diseases merits thorough examination. [19].

When considering low GI diets as risk-preventative or therapeutic during pregnancy an important factor not to be discarded is the extent and the amount of low GI foodstuff. For example, a diet extremely rich in fiber in the expense of other macro- and micronutrients may have detrimental effects on the health of the mother and the offspring. Furthermore, not all low-GI foods are a healthy option [92]. Therefore, the use of the GI would be best considered in the context of the diet's carbohydrate type as well as overall nutrient composition.

Important issues such as the level of difficulty of following a therapeutic diet have been under-researched. In one of the few examples of a study incorporating practical issues, women with low GI found the diet easier to follow and showed higher compliance and acceptability compared with the high GI diet group [85]. Such evidence is of great importance when discussing implementation of public health strategies and should be given greater consideration in future clinical studies.

The "fetal origins of disease" literature has indeed demonstrated that hormonal and nutritional aspects of the intrauterine environment can permanently alter the metabolic program of the individual. Much less attention, however, has been given to the possible genetic links between the processes of early growth and later disease as well as their interaction with nutrition (nutrigenomics). For example, telomeres (i.e. non-coding functional DNA repeat sequences at the ends of chromosomes) indicate replicative power and cellular senescence; telomeres are affected by growth variation, both prenatally and postnatally and could be targets of future research [93, 94]. Within individuals, telomere length

tracks with cardiovascular health, MetS and aging. Therefore, telomere length can be a marker of both growth history (cell division) and tissue function (senescence), which has not been studied in relation to nutrition [93] and may be a useful parameter describing the destiny of the offspring. Future studies should evaluate the importance of this parameter.

The importance of a balanced maternal diet is emphasized, especially in terms of carbohydrate quality in pregnancy and lactation, for the prevention of diet-induced adiposity and associated metabolic disruptions in the offspring. However, more longitudinal studies are required to ascertain which aspects of carbohydrate nutrition are linked to the development of the MetS. Additionally, further research is required to define the optimal range of maternal glucose, which results in a good pregnancy outcome.

Cost-effective screening strategies for early detection of children at risk, as well as long-term observational and interventional studies around conception and during pregnancy are needed. This will help provide appropriate knowledge to target susceptible mothers and offspring for metabolic disturbances in later life.

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