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Review

Maternal dietary glycemic index and glycemic load and later risk of obesity: a review of the evidence

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Summary. In view of the rising globalization of obesity, numerous studies have been performed to determine the risk factors of this epidemic. Mounting evidence suggests maternal nutrition during pregnancy may have profound effects on adult's obesity. This study aimed to summarize the current evidence regarding the association between maternal dietary glycemic index (GI) and glycemic load (GL) and obesity risk in later life, either in childhood or adulthood. A literature search using scientific databases was conducted without restriction. Included studies (n=9) were a combination of observational, interventional and animal investigations. Among human studies, one observational and two interventional studies showed a positive and others found no or negative (n=1) association between maternal dietary GI and offspring anthropometric parameters at different ages; although sometimes it was dependent to sex or timing of the maternal exposure to high GI and GL. Two of the included studies, which were animal based, also showed a beneficial effect of maternal low GI on postnatal growth rates and adiposity. Maternal low GI and GL probably have favorable effects on later obesity risk; however, the present research findings are not sufficient to conclude an approved association. More studies are necessary for scrutiny judging about the effectiveness of maternal GI and GL on offspring obesity.

Key words: glycemic index; glycemic load; maternal diet; obesity

Introduction

Obesity, a multifactorial disease, has almost doubled worldwide since 1980 (1), and results from a complex interaction of many genetic and environmental factors (2,3). It is well established that environmental factors in early life and in utero can increase susceptibility of the offspring to chronic disease, including cardiovascular disease, type 2 diabetes and obesity in later life (4). Maternal nutrition and metabolic condition are two of these factors play a key role in the long-term health and destiny of the offspring (5,6)

The maternal glucose pool is the major source of fetal fuel for growth (7). Fetal blood concentration of glucose is only 0.5 mmol/l lower than maternal blood glucose and with elevating maternal blood glucose fetal blood glucose levels raise, too (8,9). According to Pedersen 'hyperglycaemia-hyperinsulinism' theory, maternal high blood glucose levels lead to fetal hyperglycaemia and subsequently stimulating β-cell hypertrophy and fetal hyperinsulinemia. Fetus's insulin, as a growth hormone, leads to increased hepatic glycogen, lipogenesis, leptin synthesis within fetal fat depots and excessive fetal growth and adiposity (Fig. 1) (10,11). Circulating levels of glucose originate either from endogenous sources or from the diet, mainly carbohydrate. Both the quantity and quality of carbohydrate can influence the postprandial plasma glucose (12). The dietary glycemic index (GI) and glycemic load (GL) are two common tools which represent the quality and quantity of the consumed carbohydrate (13,14).

Dietary GI is defined as the ratio of the area under the glucose response curve following the intake of 50 g of digestible carbohydrate compared with a

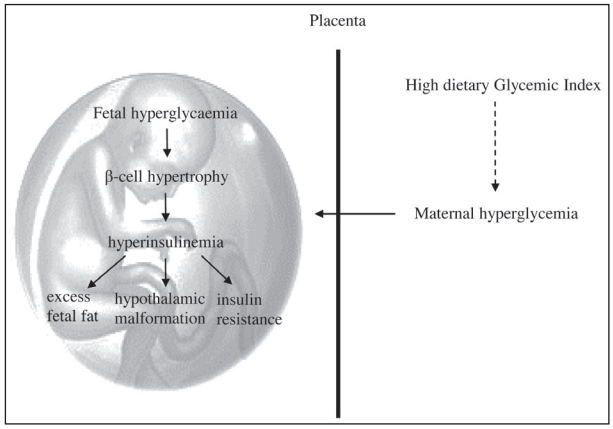

Figure 1. The possible fetal effects of maternal dietary glycemic index

similar amount of reference food, either white bread or pure glucose (13). The glycemic load is the dietary GI × amount of available consumed carbohydrate and so it is a quantitative measure of carbohydrate (14). It is believed that pregnancy does not alter the glycemic indices of the foods (15). A low GI or GL diet during pregnancy, due to its favorable effects on maternal postprandial glycemic control, is supposed to be associated with lower maternal weight gain (16), glucose concentration (17), offspring birth weight, adiposity (18,19), and maybe later risk of obesity (20,21), However, studies have no consistent results (22,23).

Fetal organs and systems mature in different critical periods during pregnancy; so short- and long-term effects of an adverse intrauterine environment on a specific organ or physiological control system depend on timing of each exposure (24). This review aimed to summarize the current human and animal evidence regarding the relationship between maternal dietary glycemic index and glycemic load (based on the exposure timing), and obesity risk in later life, either in childhood or adulthood.

Methodology

A literature review of PubMed, Cochrane Library and Science Direct was conducted without language restrictions and using various combinations of the following keywords through March 2016: glycemic, glycemic index, glycemic load, glycemic intake, glycaemic index, glycaemic load, maternal, carbohydrate, weight, obesity, overweight, adiposity, childhood, offspring, pregnancy and pregnant. A manual search of references cited by the other relevant studies was also performed. Publications that aimed to investigate the relationship between maternal dietary glycemic index or glycemic load and offspring anthropometric parameters in later life were included in the review.

Results

We initially identified 398 studies. After title and abstract review, 388 studies were excluded, and ten (eight human and two animal) studies met our search criteria (20, 21, 23, 25-30). One study (31), was also excluded due to overlap with the study by Kizirian *et al.* (30). and finally, nine articles underwent full-text review. Figure 2 shows the article selection process, and characteristics of the studies included in this review are described in Tables 1-3.

Observational studies

All three identified prospective cohort studies have not demonstrated any associations between maternal dietary GI in late pregnancy and offspring anthropometric parameters at different ages (Table 1) (21,23,25).

Okubo *et al.* (21) included the largest number of mothers (906 mother-child pairs) and assessed mater-

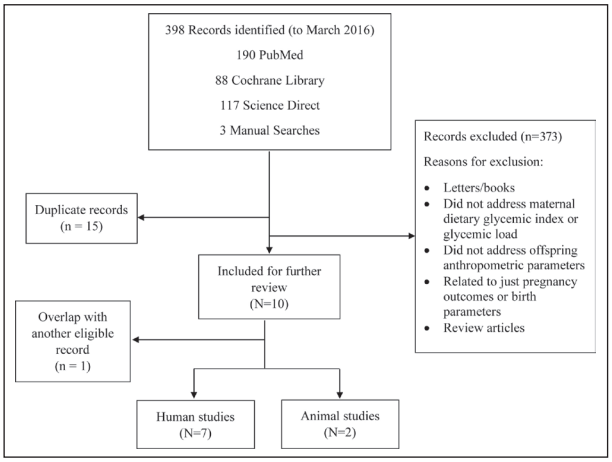

Figure 2. Study flow diagram

Table 1. Baseline characteristics of observational studies included in this review

First Author, year (ref)	Study design	exposure variables	Outcome measure	Adjustments	Study Results
Okubo, 2014 (21)	Mother-child pairs (n= 906). Dietary assessment: FFQ, at 11 and 34 week of gestation, according to the previous 3 months diet	GI by quarters Q1: 48.9–57.6 Q4: 61.5–71.7 GL by quarters Q1: 99–157 Q4: 184–334	DXA- assessed body composition at 0, 4 and 6 years old	Child's sex, age, height, birth weight, duration of breast-feeding, physical activity and dietary GI and GL at 3 y old. Maternal age at delivery, height, total energy and fiber intake, smoking, educational level, parity, circulating vitamin D and n-6 PUFA levels, gestational weight gain and prepregnancy BMI	Maternal GI and GL in early, but not later pregnancy were associated with greater fat mass at 4 and 6 years old but not at birth.
Poon, 2013 (23)	Mother-infant pairs (n= 893). Dietary assessment: modified FFQ between 28 and 36 weeks of gestation	GI by tertiles T1: 35–48 T3: 52–63 GL by tertiles T1: 38–107 T3: 153–520 and two other dietary pattern indices (AHEI-P and aMED)	Birth weight and early infant growth between 4–6 months	Maternal total energy intake, age, race, education, poverty index ratio, prepregnancy BMI, smoking and alcohol consumption during pregnancy, gestational age and infant's WFL z-score at birth	There was no relation between birth weight or early infant growth and GI or GL.
Danielsen, 2013 (25)	Mother-offspring pairs (n= 428) Dietary assessment: semi-quantitative FFQ, at 30-week gestation	GI and GL by quintiles GI: 49.3-88.3 GL: 108.6-267.6	Offspring anthropometric (Height, weight and waist circumference) and metabolic measurements at 20 years old	Maternal smoking, height, pre-pregnancy BMI, education and energy intake and offspring sex and current physical activity	An increase of GI as much as 10 units was associated with increased total cholesterol, HOMA-IR, insulin and leptin among offspring as much as 3, 9, 9, and 21%, respectively. An increase of GL as much as 10 units was associated with a higher waist circumference among the female offspring as much as 0.26 cm.

FFQ: Food Frequency Questionnaire, GI: Glycemic index, GL: Glycemic Load, DXA: Dual energy X-ray Absorptiometry, PUFA: Polyunsaturated Fatty Acids, BMI: Body Mass Index, AHEI-P: Alternative Healthy Eating Index for Pregnancy, aMED: Alternate Mediterranean Diet, WFL: Weight-For-Length, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table 2. Baseline characteristics of interventional studies included in this review

First Author, year (ref)	Study design	Outcome measure	Adjustments	Study Results
Kizirian, 2016 (30)	a longitudinal follow-up study in a subgroup of mother-infant pairs (n =59, pregnant women were at high risk of GDM) participating in a larger randomized trial who had followed: A low-GI diet (LGI) (n=30) A high-fiber, moderate-GI diet (HF) (n=29) Dietary assessment: 3-day food diaries at baseline (12–20 wk of gestation) and at the end of the intervention (34–36 wk of gestation)	Infant anthropometric measurements, at birth and every month for 6 mo and then at 9 and 12 mo of age, body composition at 0, 3, 6 and 12 mo, aortic intima-media thickness at 12 mo	maternal prepregnancy BMI, gestational weight gain, gestational age, GDM, sex, and infant feeding practice	A decrease of dietary GI as much as 6 units resulted in lower offspring WAZ and LAZ at birth (the values became closer to the population norms) and lower aortic wall thickness at 12 mo of age, but no difference in adiposity, weight gain or growth trajectory during the first 12 mo after birth was seen between groups.
Horan, 2015 (20)	Women who had a history of macrosomic baby randomly allocated to: Women in the control group who received usual antenatal care (n=142) Women in the intervention group who advised to consume low GI diet at 14th week of pregnancy (n= 138). Dietary assessment: 3-day food diaries during each trimester.	Maternal and offspring anthropometry at 6 months post-partum	Maternal education level, infant's age, gender, birth weight and breastfeeding duration	Maternal dietary GI of third trimester was positively related to offspring adiposity while trimester 1 GI was negatively associated with waist to hip circumference ratio.
Louie, 2015 (29)	Women with GDM at 29th weeks of gestation were assigned to: A low-GI diet (LGI) (n = 33), A conventional high-fiber diet (HF) (n = 25) Dietary assessment: 24-h recall, every 2–3 weeks and a 3-day food record at the end of the intervention	Maternal and offspring anthropometry at 3 months post-partum and maternal biochemical parameters	breastfeeding status (exclusive vs. non-exclusive), infant age and gender	A decrease of dietary GI as much as 6 units made no differences in maternal and offspring outcomes.
Moses, 2007 (28,32)	A longitudinal follow-up study in a subgroup of pregnant women (n =43) participating in a larger randomized trial that followed: A low GI (n=23) A moderate-to-high GI diet (n=20) Dietary assessment: 3-d food record and diet history at the baseline, at the end of intervention and after 22 mo, a 24-h diet recall at ≈22 and 30 wk gestation	infant size (weight and height) at birth and 22 mo post-partum	age of the infant and months of breastfeeding	Higher GI diet resulted in higher birth centile, higher rate of LGA and heavier infants at a mean of 22 mo.

GDM: Gestational Diabetes Mellitus, GI: Glycemic Index, wk: week, WAZ: Weight-for-age z score, LAZ: Length-for-age z score, mo: month, BMI: Body Mass Index, LGA: Large for Gestational Age.

Table 3. Baseline characteristics of animal studies included in this review

First Author, year (ref)	Study design	exposure variables	Outcome measures	Study Results
Gugusheff, 2015 (27)	female Albino Wistar rats (n=28) and their offsprings (n=56)	A low or high GI diet at least 4 weeks before mating and throughout pregnancy and lactation and also post-weaning	Fat deposition, glucose tolerance, hepatic fat content and gene expression in the offspring at both 3 and 12 weeks	Female offspring of low GI dams had lower visceral adiposity and higher glucose tolerance at 3 weeks and lower relative interscapular fat mass at 12 weeks.
Smith, 2009 (26)	Sheep (n= 104) and their lambs (n= 104)	oral administration of: 1) 100 ml of propylene glycol (PG) 2) 100 ml of water (control) twice per day from the onset of the third trimester until delivery	Plasma and body dimensions measurements of the lambs at 0, 6 and 12 weeks	An increasing maternal GI diet resulted in increased birthweight and faster postnatal growth rates in lambs, until 12 weeks.

GI: Glycemic index, GL: Glycemic Load

nal dietary GI and GL at 11 and 34 wk of gestation. After adjusting for a large number of potential confounding factors, they found a positive association between maternal dietary GI and GL in early pregnancy and dual-energy X-ray absorptiometry (DXA) which assessed adiposity at 4 and 6 years old [fat mass SDs per 10-unit GI increase: β = 0.43 (95% CI: 0.06, 0.80), P = 0.02 at 4 y old; β = 0.40 (95% CI: 0.10, 0.70), P = 0.01 at 6 y old; fat mass SDs per 50-unit GL increase: β = 0.43 (95% CI: 0.19, 0.67), P < 0.001 at 4 y old; β = 0.27 (95% CI: 0.07, 0.47), P = 0.007 at 6 y old]. In this study, however, maternal dietary GI in late pregnancy was also related to fat mass at four and six years old, but these associations were disappeared after controlling for confounding factors.

In 2013, Poon *et al*. (23) have published an article based on a prospective cohort study (The Infant Feeding Practices Study II) to investigate the association between overall maternal dietary patterns and also dietary GI and GL during their 3rd trimester with birth weight and early infant growth by 4–6 months. The results of this study showed no association between either maternal carbohydrate quality and quantity (as measured by GI and GL) nor dietary pattern and birth weight, relative risk of abnormal size-for-gestational age (small or large) and infant growth in the first 4–6 months.

Another study by Danielson *et al*. (25) showed no associations between maternal dietary GI during third trimester and offspring anthropometric measures at 20 years, and GL was positively related to higher waist circumference only in female offspring (difference per 10-unit GL increase: 0.26 cm; 95% CI: 0.01, 0.51).

Interventional studies

Four controlled trials were identified (three in normal pregnancy and one in pregnancy complicated by gestational diabetes mellitus) with inconsistent results.

In a recent study by Kizirian *et al*. (30) a longitudinal follow-up study was performed in a subgroup of mother-infant pairs, participating in a larger randomized trial which compared the effects of a low-GI diet and a conventional high-fiber (HF) diet during pregnancy on perinatal outcomes. They found no difference in adiposity, weight gain or growth trajectory during the first 12 mo after birth between groups.

Similarly, in the other randomized controlled trial, Louie *et al.* (29) for the first time, examined the effect of a low GI diet during gestational diabetes mellitus (GDM) on maternal and infant outcomes at 3 months post-partum. Pregnant women were assigned as GDM at 29 weeks of gestation and followed either a low glycemic index (LGI) or a conventional high-fiber diet (HF). They demonstrated that a six-unit decrease of dietary GI made no differences in maternal and offspring anthropometry at 3 months post-partum.

Horan *et al*. (20) have performed a secondary analysis in the ROLO data to study the effect of a low GI diet in secundigravida women, with a previous macrosomic baby, on offspring adiposity at 6 months. They have found a positive association between maternal dietary GI of third trimester and triceps and biceps skinfold thickness for age z-score in her infant at 6 months (Respectively, B = 0.053, p = 0.023 and B = 0.121, p = 0.003), while dietary GI of first trimester was negatively associated with waist to hip circumference ratio (B = –0.004, p = 0.004).

In 2007, Moses et al. reported a lower rate of large-for-gestational age (LGA) infants and subsequently a lower weight at a mean of 22 mo in offspring whose mothers followed a low-GI diet from the beginning of the second trimester until delivery (Table 2) (28, 32).

Two animal studies have been also published about the aim of this review, which have shown a positive association between maternal dietary GI and adiposity or growth rates in later life.

In a recent study by Gugusheff *et al*. (27) female Albino Wistar rats were assigned to either a low or high GI diet, at least 4 weeks before mating and throughout pregnancy and lactation. In weaning period, pups were also provided with either the same diet as their mother or the alternate diet until 12 weeks of age. The results of this study showed that only female offspring of low GI dams had lower visceral adiposity (0.45 ± 0.03 *vs*. 0.53 ± 0.03% body weight, P< 0.05) and higher glucose tolerance (AUC [glucose], 1243 ± 29 *vs*. 1351 ± 39 mmol min/l, P<0.05) at 3 weeks and lower relative interscapular fat mass, independent of their post-weaning diet, at 12 weeks of age.

Smith *et al*. (26) have designed another study on pregnant ewes to compare the effect of oral administration of 100 ml of water *vs*. propylene glycol twice per day, in the last trimester of pregnancy. They have demonstrated that high GI diet resulted in increased birth weight (5.27 ± 0.22 *vs*. 5.01 ± 0.02 kg, P= 0.032) and faster postnatal growth rates of lambs until 12 weeks (0.31 ± 0.02 *vs*. 0.29 ± 0.02 kg/day, P= 0.002). Moreover lambs of ewes given high GI diet, reached the same carcass weight at an earlier age (*P* = 0.039) compared to lambs of control ewes.

Discussion

In this review, we evaluated seven human and two animal studies. Among human studies, one observational and two interventional studies showed a positive and others found no or negative (n=1) association between maternal dietary GI and offspring anthropometric parameters at different ages; although sometimes it was dependent to sex or the timing of maternal exposure to high GI and GL. In one of the human studies, a positive association was only seen between maternal dietary GL and female waist circumstance in later life. Two of the included studies, which were animal based, also showed a beneficial effect of maternal low GI on postnatal growth rates and adiposity. The current evidence is not sufficient to conclude an approved association, but it seems that maternal low GI and GL could have favorable effects on later obesity risk.

It is well recognized obesity depends on a genetic basis which is affected by environmental risk factors, especially nutrition and lifestyle (2). In addition, substantial evidence has shown susceptibility of genes associated with the risk of obesity, to epigenetic mutations and suggested gestational milieu and maternal diet can alter the epigenetic regulation of the developing fetus, which affect its risk factors for obesity later in life (33, 34). As an example, Allard *et al*. found that higher maternal fasting glucose at second trimester was associated with lower methylation of the offspring leptin gene and higher cord blood leptin levels, which was related to long term programming of adiposity in later life (35).

Maternal high blood glucose levels, even in normal range, have been supposed to lead to fetal hyperinsulinemia and subsequently to higher fetal growth and adiposity (10). In addition, maternal hyperglycemia could make a perinatally acquired hypothalamic malformation and/or insulin resistance that leads to permanent increased levels of orexigenic neurotransmitters and decreased levels of satiety signals in the developing fetus (36,37). Therefore, a low GI or GL diet during pregnancy, due to its favorable effects on maternal postprandial glycemic control, is supposed to be associated with lower fetal adiposity. In this regard, maternal dietary GI and GL during pregnancy,

have been positively linked to offspring birth weight in some (16, 32) but not all (22, 38), studies. Kizirian et al found that in women at high risk of GDM, a lower dietary GI resulted in lower (and more normal) offspring weight-for-age z score at birth (30). On the other hand, based on some evidence, there is a linear and positive association between birth weight and subsequent BMI and overweight in children and young adults, however it is J- or U-shaped in others (4, 39). So a positive association between maternal GI and GL and later obesity risk is expected. It is known that other maternal characteristics including prepregnancy BMI, gestational weight gain, lifestyle and dietary factors, also exert a profound influence on offspring birth weight and later adiposity (40-42).

An analysis of research methods indicated that in the most articles reviewed, the effect of maternal dietary GI and GL has been assessed on the offspring early growth rates; which could be a dominant risk factor for adult obesity, partly due to hormonal programming (43-46). Among three observational studies we have reviewed, though anthropometric indices were measured using different methods, all of them showed no associations between maternal dietary GI in late pregnancy and offspring adiposity in different ages. In one observational research, a direct association between maternal GI and GL, in early pregnancy, and DXA-assessed fat mass at 4 and 6 years old was reported (21); while Horan *et al*. showed an inverse effect of dietary GI of first trimester on waist to hip circumference ratio at 6 months, in their interventional study (20). All above reviewed interventional studies evaluated the effect of maternal dietary GI during second or third trimester, which two of them found a positive influence of maternal GI on offspring growth rates.

Possible explanations for different findings of mentioned studies, are heterogeneities in methodology (design of the study, age of the infants at the time of the measurements, methods of measuring obesity, etc.), population and confounding factors considered. There are many cofactors that may affect mentioned association, which some human studies did not consider them. Birth weight, duration of breastfeeding, social characteristics, maternal diet quality during the pregnancy and also post-partum, offspring's own diet and activity and other genetic or environmental risk factors are some of these cofactors.

In addition to timing of the maternal exposures during pregnancy, offspring sex seems to be important in the programming of adult disease susceptibility, as Ravelli *et al*. have described before (47). In this study, prenatal exposure to the Dutch famine in early gestation was related to higher BMI and waist circumference in 50-y-old women, but not men, maybe through offspring perturbations of central endocrine regulatory systems. Evidence suggests that fetal sex differences may have dissimilar effects on the transgenerational epigenetic response to the same maternal diet and environment (48-50). Moreover, sex specific function of the human placenta may contribute to the differences in fetal growth (51).

It is important to be mindful that there are some criticisms about the inability of GI to predict healthy foods, its inaccurate and imprecise measuring method and its failure to justify the insulin response (52-54). Wolever believes that some of these criticisms are based on flagrant errors in comprehension, quotation and interpretation of GI (55). Nevertheless it is clear that GI values of foods may vary depending on the differences in variety, brand name, processing, cooking, cultivation, growing conditions and etc. (56, 57); for this reason, GI databases, that may differ from one study to another, can't be completely accurate (57).

Based on the currently available data, the use of a low-GI diet during pregnancy would seem to have no adverse outcome (58, 59). Scholl *et al*. (18) reported a twofold increased risk of a small-for-gestational-age birth with a maternal lower dietary GI, but not GL, during the third trimester; Although they did not observe concomitant increased risk of LGA with a high GI maternal diet. This prospective study was performed on underprivileged women who were reported a diet rich in sugars. Simple sugars have a lower GI than refined starchy foods (60, 61), so lower maternal dietary GI could represent higher intake of sugars and overall poor dietary quality which per se could lead to low birth weight. As Lenders et al. pointed out that consuming high sugar diets by low-income pregnant adolescents are related to increased risk for lower birth weight (62).

The newness of this research field and growing interest about it, respectively, may be the reasons for the

few, but new published research up to now. According to these evidence, maternal low dietary GI and GL may aid in reducing risk of obesity in later life, nevertheless maternal food choices should be in the context of the quality and overall nutrient composition of the diet, not only its GI.

Conclusion

According to the few available studies, maternal low glycemic index and glycemic load diet seem to have favorable effects on later obesity risk; however, offspring sex and timing of the maternal exposure to high or low GI are important. Overall, the present findings are not sufficient to conclude an approved association. So larger studies, especially randomized controlled trials, are required to distinguish the precise association and pursue preventive strategies for later obesity.

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