

Review Article

The influence of maternal glycaemia and dietary glycaemic index on pregnancy outcome in healthy mothers

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Infant birth weight has increased in Ireland in recent years along with levels of childhood overweight and obesity. The present article reviews the current literature on maternal glycaemia and the role of the dietary glycaemic index (GI) and its impact on pregnancy outcomes. It is known that maternal weight and weight gain significantly influence infant birth weight. Fetal macrosomia (birth weight >4000 g) is associated with an increased risk of perinatal trauma to both mother and infant. Furthermore, macrosomic infants have greater risk of being obese in childhood, adolescence and adulthood compared to normal-sized infants. There is evidence that there is a direct relationship between maternal blood glucose levels during pregnancy and fetal growth and size at birth, even when maternal blood glucose levels are within their normal range. Thus, maintaining blood glucose concentrations within normal parameters during pregnancy may reduce the incidence of fetal macrosomia. Maternal diet, and particularly its carbohydrate (CHO) type and content, influences maternal blood glucose concentrations. However, different CHO foods produce different glycaemic responses. The GI was conceived by Jenkins in 1981 as a method for assessing the glycaemic responses of different CHO. Data from clinical studies in healthy pregnant women have documented that consuming a low-GI diet during pregnancy reduces peaks in postprandial glucose levels and normalises infant birth weight. Pregnancy is a physiological condition where the GI may be of particular relevance as glucose is the primary fuel for fetal growth.

Birth weight: Macrosomia: Diet: Glycaemic index: Infants: Pregnancy

Infant birth weight has increased in Ireland in the past 30 years⁽¹⁾. It is known that maternal weight at the time of conception and maternal weight gain from early to late pregnancy exert a profound influence on infant birth weight^(2–4). To further support this, data from an Irish cohort illustrated that fetal macrosomia (birth weight >4000 g or birth weight above the 90th percentile for gestational age) recurs in a second pregnancy in one-third of women whose first infant was macrosomic⁽⁵⁾. Additionally, maternal weight was noted to influence the recurrence of fetal macrosomia. Women who delivered a second macrosomic infant had greater pre-pregnancy weight and greater weight gain during pregnancy than women in whom macrosomia did not recur⁽⁵⁾. Rates of childhood overweight and obesity have concurrently risen in Ireland within the past two decades⁽⁶⁾, with approximately one in five Irish children between 5 and 12 years being overweight or obese⁽⁷⁾. There is evidence to suggest that fetal macrosomia is a risk factor for childhood obesity, and intra-uterine life has been described as a 'critical period' for the development of obesity in

adulthood⁽⁸⁾. Efforts to improve obesity treatment and prevention are now a major public health priority in Ireland. Fetal macrosomia is related to a higher incidence of adverse obstetric outcomes, including maternal anal sphincter injury⁽⁹⁾ and adverse neonatal outcomes, notably shoulder dystocia^(10–12). Additionally, longitudinal evidence has shown that infants born at the highest end of the distribution for weight have greater risk of childhood obesity and are more likely to develop obesity-related diseases such as CVD, diabetes mellitus (DM) and hypertension in later life, compared to normal-sized infants^(13,14). Observational evidence suggests that faster growth during infancy and childhood is related to an increased risk of adult obesity^(14–17), indicating that interventions to alter growth during infancy and childhood could prevent adult obesity. However, few studies have accounted for the various confounding factors that influence birth weight, namely, gestational age, parental body weight and height, and socioeconomic status. Thus, it is not yet clear how early in life obesity prevention should begin.

Abbreviations: CHO, carbohydrates; DM, diabetes mellitus; GI, glycaemic index; GL, glycaemic load; LGA, large-for-gestational-age infant.

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Maternal glucose homeostasis in pregnancy

In humans, the main source of glucose comes from the maternal diet, predominantly from carbohydrates (CHO). Both the amount and type of CHO can have different effects on blood glucose levels^(18–20). During pregnancy, all metabolic functions increase to meet the demands of the growing fetus, placenta and uterus. However, CHO metabolism exhibits the most dramatic change⁽²¹⁾. Pregnancy induces profound metabolic changes in all women, whether they have diabetes or not, and these metabolic changes become more evident as pregnancy progresses, particularly in women consuming a typical Western diet, rich in refined and processed CHO⁽²²⁾. Insulin secretion doubles between the first and third trimesters. Insulin resistance appears to worsen as pregnancy progresses, yet this seems to be a normal physiological adaptation that restricts maternal glucose uptake to guarantee sufficient glucose availability for the growing fetus⁽²³⁾. It is usually women who are insulin resistant before pregnancy who go on to develop gestational DM⁽²³⁾. The exact aetiology of insulin resistance during pregnancy is unknown; however, it is most likely mediated by increasing levels of pregnancy-associated hormones including human placental lactogen, insulin-like growth factor-1 and human placental growth hormone⁽²³⁾. Normal glucose ranges during pregnancy are 3.4–5.5 mmol/l except immediately after meals when levels can go up to 6.5 mmol/l⁽²⁴⁾. In response to a glucose load, the following are limits of normal ranges of glucose levels: based on US recommendations using a 100 g glucose load, a normal glucose response in pregnancy is defined as <5.8 mmol/l fasting, <10.6 mmol/l 1-h, <9.2 mmol/l 2-h and <8.1 mmol/l 3-h postprandial⁽²⁵⁾. Alternatively, the WHO recommend using a 75 g glucose load and with the cut-offs being <7.8 mmol/l fasting and \leq 11.1 mmol/l and >7.8 mmol/l 2-h postprandial⁽²⁶⁾.

Fetal glucose homeostasis

Plasma glucose levels in the fetus follow a similar pattern to those in the mother, with a difference of about 0.5 mmol/l in favour of the mother. This difference increases as the mother becomes more hyperglycaemic, both in diabetic and non-diabetic women. Insulin is seen in the fetal circulation during the first trimester of pregnancy and levels often become elevated later on in diabetic pregnancies, but it does not cross the placenta at normal concentrations. It is thought that in the fetus of a non-diabetic mother, insulin is likely used as a growth-promoting hormone⁽²³⁾. However, in diabetic pregnancies, there is a sharp increase in fetal insulin concentrations in response to glucose. Pedersen 'hyperglycaemia-hyperinsulinism' theory proposes that maternal hyperglycaemia gives rise to fetal hyperglycaemia, which stimulates β -cell hypertrophy and the secretion of excess insulin⁽²³⁾. It also explains much aetiology of fetal pathology of diabetic pregnancies. Longitudinal evidence suggests that infants born small-for-gestational-age have fewer β -cells in their pancreas and are more likely to become overweight as adults with greater risk of developing insulin resistance and type 2 DM⁽²³⁾. Thus, normalising the glucose environment of the fetus may reduce the tendency to hyperinsulinaemia and hence reduce the incidence of

many perinatal problems and possibly reduce the incidence of metabolic diseases in later life⁽²³⁾.

Maternal glycaemia, fetal growth and pregnancy outcomes

The principal environmental factor regulating fetal growth is maternal substrate delivery to the placenta; thus, factors that modify either the rate of placental blood flow or maternal blood glucose levels can alter the rate of fetal growth^(27–29). Blood glucose levels can be assessed during pregnancy, and a direct relationship between maternal blood glucose concentrations within the normal range and infant birth weight exists⁽³⁰⁾. Sharp reductions in maternal energy intake lower maternal blood glucose levels, fetal growth rate and infant birth weight^(31,32). On the other hand, sustained high maternal blood glucose levels during pregnancy may lead to fetal overgrowth and increases the risk of delivering a large-for-gestational-age infant (LGA) (birth weight above the 90th percentile for gestational age)⁽³³⁾. In both human and animal models, maternal 24-h blood glucose levels, especially in late pregnancy, are positively associated with fetal growth and size at birth^(18,32–34). Interestingly, normoglycaemia is correlated with normal levels of other nutrients, including amino acids and lipids⁽³⁵⁾. Paradoxically, however, very few studies have been carried out thus far to define the optimal range of maternal glucose, which results in a good pregnancy outcome.

The recent Hyperglycemia and Adverse Pregnancy Outcomes study has investigated whether maternal hyperglycaemia, less severe than that in DM, was associated with increased risks of adverse obstetric outcomes⁽³⁶⁾. The present large-scale observational study took place in nine countries and included over 23 000 pregnant women who underwent 75 g oral glucose tolerance testing between 24 and 32 weeks of gestation. Height, weight and blood pressure were measured at the visit; information on smoking, alcohol use, family history of DM and other demographic factors were gathered by means of a standardised questionnaire; and race/ethnicity was self-reported by the participants. All plasma glucose levels were measured at one central laboratory to avoid confounding effects of analytic variation among centres⁽³⁶⁾. The primary outcomes included the following: birth weight above the 90th percentile for gestational age; primary caesarean delivery; clinical neonatal hypoglycaemia; cord blood serum C-peptide level above the 90th percentile (fetal hyperinsulinaemia). Secondary outcomes included the following: premature delivery (<37 weeks of gestation); shoulder dystocia or fetal injury at birth; the need for neonatal intensive care; hyperbilirubinaemia; pre-eclampsia⁽³⁶⁾. The authors of Hyperglycemia and Adverse Pregnancy Outcomes reported strong associations between increasing levels of maternal fasting, 1-h, and 2-h plasma glucose after a 75 g oral glucose tolerance test and infant birth weight above the 90th percentile. Weaker associations were observed between increasing maternal plasma glucose levels and primary caesarean delivery and clinical neonatal hypoglycaemia⁽³⁶⁾. Positive associations were also identified for secondary outcomes. These findings indicate that maternal blood glucose levels below those diagnostic of DM are linked to adverse pregnancy outcomes. They also point out the urgent need to reconsider

current criteria for diagnosing and treating hyperglycaemia in pregnancy⁽³⁶⁾.

A longitudinal study by Parretti *et al.*⁽³⁷⁾ carried out from June 1998 to December 1999 included fifty-one pregnant women with normal glucose challenge tests. The participants were asked to consume three main meals at specific times each day and to carry out daily glucose profiles fortnightly between 28 and 38 weeks of gestation without changing their lifestyle or dietary habits. All participants were taught how to monitor their own blood glucose levels using a reflectance meter. Blood glucose levels were recorded before meals, 1 and 2 h postprandially, and every 2 h in the afternoon and overnight. Fetal parameters included biparietal diameter, head circumference, abdominal circumference, head:abdominal circumference ratio (head circumference: abdominal circumference) and femur length, and were assessed by ultrasound scans at 22, 28, 32 and 36 weeks of gestation⁽³⁷⁾. The results revealed significant positive associations between postprandial blood glucose levels and measures of fetal adiposity, particularly 1-h postprandial glucose and fetal abdominal circumference. It is also worthy to note that mean postprandial glucose levels did not exceed 6.0 mmol/l (1081 mg/l), a level which is considerably lower than current thresholds for good glucose control in pre-gestational diabetic pregnancies. This suggests that merely blunting the peak postprandial glucose response may control fetal growth within the normal range⁽³⁷⁾. Thus, maintenance of blood glucose concentrations within normal parameters during pregnancy may also reduce the incidence of adverse obstetric outcomes.

Diet and insulin sensitivity during pregnancy

Fraser *et al.*⁽¹⁹⁾ conducted a randomised study in the UK, where the metabolic effects of three diets were investigated in fifteen non-pregnant women and fourteen pregnant women in their third trimester. The women were of normal weight, non-smoking and non-diabetic. Each participant was randomised to one of three dietary patterns. Diet 1 resembled a 'normal European' intake (containing 40% energy from CHO and 10 g dietary fibre); diet 2 also encompassed a normal European intake, but replaced refined CHO with high-fibre CHO (40% energy from CHO and 52 g dietary fibre); and diet 3 represented a 'normal African' intake with almost all energy available from complex CHO (60% energy from CHO and 84 g dietary fibre). Following a 2-week habituation period, the women were instructed to follow the dietary pattern for 2 weeks, after which they spent a day in the research unit where they consumed standardised meals that corresponded with the dietary pattern of randomisation⁽¹⁹⁾. Fasting blood glucose levels were obtained upon arrival and subsequent samples were taken hourly. After a sampling period, participants were given a different dietary pattern to follow for the next 2 weeks and so on until all participants had followed each dietary pattern for 2 weeks. Thus, blood profiles were obtained from the pregnant women at 32, 34 and 36 weeks of gestation. The results showed a loss of insulin sensitivity in the pregnant women following diet 1, but not in those following diets 2 or 3. The authors concluded that the loss of insulin sensitivity, typical of Western women in late pregnancy,

may be diet-induced⁽¹⁹⁾. The higher fibre and lower glycaemic intakes of diets 2 and 3 may have blunted the mid-late pregnancy increases in insulin resistance⁽¹⁹⁾. Even though fibre intake in the typical Western diet is substantially lower than amounts consumed in diets 2 and 3 in the present study, increasing intakes could help to blunt pregnancy-related insulin resistance.

The glycaemic index

It is recognised that different CHO foods produce different glycaemic responses⁽³⁸⁾. The classification of CHO foods according to their glycaemic responses was first introduced by Otto *et al.* in the 1970s^(39,40). Following on from this, Crapo *et al.*^(41–43) also found differences between the glucose responses of different CHO foods. It was Jenkins and colleagues^(44,45) in 1981 who conceived the concept of the glycaemic index (GI) as a tool for assessing and classifying the glycaemic responses of CHO foods, and it has since been used as a tool for the dietary management of DM, and later dyslipidaemia.

The GI is defined as 'the incremental area under the blood glucose response curve of a test food containing 50 g available CHO expressed as a percentage of the response to the same amount of available CHO from a reference food'⁽⁴⁴⁾. Jenkins⁽⁴⁴⁾ landmark study in 1981 compared 50 g portions of sixty-two common CHO-rich foods to 50 g glucose. The area under the blood glucose response curve for each food tested was calculated and expressed as a percentage of the area obtained after ingesting 50 g glucose. The higher the area under the blood glucose response curve, the higher the GI of a food. The common standard against which foods are compared is either glucose or white bread^(46–50). If white bread is used as the reference food, the GI value obtained must be divided by 1.4 to get the GI value contrast to glucose⁽⁵¹⁾. Over 2400 different foods have now been tested for their GI value. Foods with a low GI are assigned a value of 55 or less, foods with a high GI are given a value of 70 or higher, and medium-GI foods have a value between 55 and 70. The underlying principle of the GI is that foods with a low GI are digested and absorbed more slowly than foods with a high GI, and therefore, help regulate blood glucose concentrations. It is important to be mindful that not all low-GI foods are necessarily a healthier option⁽⁵¹⁾. Therefore, it may be imprudent to base food choices solely on GI values. Application of the GI should be in the context of the overall nutrient composition of the diet, paying attention to the quality of CHO foods, while other dietary factors like energy density, fibre content and antioxidants should also be regarded⁽⁵¹⁾.

Questions were raised over whether or not the amount of CHO consumed is more important than the type of CHO consumed. To eliminate these concerns, researchers at Harvard University developed the concept of the glycaemic load (GL) in the 1990s. The GL is the mathematical product of the GI of a food and its CHO content (g) divided by 100 ($GL = GI/100 \times \text{amount of available CHO}$). Foods with a low GL have values between 1 and 10; medium GL between 11 and 19; and high GL 20 or greater. GI values may have completely different GL values and vice versa⁽⁵²⁾. However, some foods such as bananas have equal GI and GL values

(both medium GI (59) and medium GL (12)). The GL can be useful in predicting the acute impact on blood glucose responses within the context of mixed meals⁽⁵³⁾, and it is believed to give a better reflection of a food's glycaemic response than the GI; however, its validity remains questioned⁽⁵⁴⁾. The use of the GI is still advocated more often than the GL. If it were not, people may strive to avoid CHO completely to achieve the lowest-GL diet possible⁽⁵⁵⁾.

The GI is complex, but its use in public health may be simple. Australian consumers have been exposed to the GI concept the longest, and they appear to have the most success at implementing GI use among its population⁽⁵⁶⁾. The introduction of the GI Symbol Programme in 2002 has increased both consumer and health professional awareness⁽⁵⁶⁾. The international tables of GI values published in 1995, 2002 and 2008 come from Australia, through the efforts of Professor Brand-Miller and her colleagues^(57–59). Globally, the picture is somewhat different, as consumer awareness varies between countries.

The impact of the glycaemic index in pregnancy

Pregnancy is a physiological condition in which the GI may be of particular relevance because maternal glucose is the preferred fuel for fetal growth. Studies in non-pregnant women have shown that modifying the type of CHO in the diet from low GI to high GI indices increases postprandial blood glucose levels by 100%⁽⁶⁰⁾. Such findings in non-pregnant women led to similar studies in pregnant women.

In 1998, Clapp⁽⁶¹⁾ employed a randomised prospective design where twelve healthy women in the USA were recruited before pregnancy and followed to delivery. The women were initially placed on an isoenergetic diet consisting of 55–60% CHO primarily composed of low-GI foods. At 8 weeks of gestation, the women were randomised either to continue with the low-GI diet or to change to an isoenergetic high-GI diet containing equivalent amounts of CHO and protein. Dietary intake was monitored twice weekly using 24 h recalls and maternal weight gain, and glucose and insulin responses to diet were measured on a monthly basis⁽⁶¹⁾. The women who were randomised to the high-GI diet displayed progressive increases in postprandial glucose responses, whereas the glucose responses of women following the low-GI diet remained the same. Remarkably, the women who consumed the high-GI diet all delivered a LGA infant with a mean weight of 1000 g more than the mean weight of infants born to women on the low-GI diet. They also gained significantly more weight during pregnancy ($P < 0.01$) than women consuming the low-GI diet. The number of women in the study was small and an exercise component was a confounding variable; however, consuming a low-GI diet blunted the mid and late pregnancy increase in insulin resistance, which is usually seen in women consuming a Westernised diet^(22,30,61). These results support the hypothesis that maternal substrate delivery is a major environmental determinant of fetoplacental growth. The test diets were isoenergetic, thereby, indicating that quality rather than quantity of food consumed is more important and may influence maternal weight gain, fetoplacental growth and infant birth weight. The authors did not document whether the dietary advice was given by a clinical or research dietitian.

In 2004, Scholl *et al.*⁽⁶²⁾ reported on a large-scale prospective observational study where 1082 pregnant women from an underprivileged area in the USA were followed throughout pregnancy. Information on socioeconomic status, demographic factors and lifestyle was collected at study entry. Pre-gravid weight was self-reported, and maternal weight was then monitored throughout pregnancy. Dietary data and GI were assessed from three 24 h recalls; however, there was no dietary intervention. Women who consumed a low-GI diet delivered infants that were >100 g smaller and also had a twofold increased risk of delivering a small-for-gestational-age infant⁽⁶²⁾. Interestingly, there were no observations that a high-GI diet led to concomitant increases in birth weight or LGA births. In the third trimester, dietary GI was found to be positively related to biomarkers of maternal CHO metabolism, including glycosylated Hb and maternal plasma glucose levels. Thus, a low-GI diet was associated with lower blood glucose levels, and a high-GI diet was associated with higher blood glucose levels. Notably, 50% of CHO consumed came from refined sugars, and, because refined sugars such as sucrose have a lower GI than white bread or glucose, it may be possible that the lower birth weights for women with the lowest-GI diet could have been influenced by both CHO and nutrient quality of the diet overall. A strength of the study was that it involved over 1000 women, but they were all from socially disadvantaged areas and this may have been another confounding factor influencing the quality of the women's diet⁽⁶²⁾.

An Australian team led by Moses *et al.*⁽⁶³⁾ employed a parallel controlled study in 2006. Sixty-two healthy pregnant women were recruited between 12 and 16 weeks of gestation and assigned alternatively to receive low-GI dietary advice or high-fibre, high-GI dietary advice. Each participant saw a research dietitian five times during their pregnancy. Food intake data were collected using two 3 d food records, two diet histories and two 24 h recalls. Maternal weight and height were measured at baseline, and maternal weight gain was monitored during the pregnancy. The mean GI of women following the low-GI diet was significantly reduced during the study ($P < 0.001$). Infants born to women following the high-GI diet were significantly heavier than infants born to women following the low-GI diet, although this level of significance was marginal ($P = 0.051$) and had a greater percentage body fat as determined by the ponderal index (birth weight (g)/length (cm)³) ($P = 0.03$), and had a higher prevalence of LGA births ($P = 0.001$). Compliance and acceptability of both diets were also examined. It is of interest to note that women following the low-GI diet found the diet easier to follow ($P = 0.048$)⁽⁶³⁾.

A recent randomised trial by Smith *et al.*⁽⁶⁴⁾ has investigated the effect of transient hyperglycaemic intakes (equivalent to consuming a high-GI diet) during the third trimester of pregnancy on offspring birth weight and ensuing growth in sheep. The study commenced on day 98 of gestation (first day of the third trimester) and continued until the first signs of parturition (approximately day 147). Fifty-one ewes were randomised to receive the intervention of 100 ml twice per day of propylene glycol, while fifty-three ewes acted as controls and received 100 ml twice per day of water. Twice during the study (days 109 and 140 of gestation), twelve ewes were selected from each group, and blood samples

were taken to determine blood glucose and insulin response to treatment. At birth, blood was collected from the lambs, and weight was measured at birth, and at 6 and 12 weeks of age. Further body dimensions included: head circumference, height, thoracic circumference, jaw circumference, crown rump length, body length and inside leg length, and were measured within 24 h of birth⁽⁶⁴⁾. Ponderal index was also calculated (birth weight (kg)/height (cm) × 100)³. Results showed that lambs born to the ewes given propylene glycol had significantly heavier birth weights ($P=0.032$), ponderal index ($P=0.043$) and plasma glucose levels ($P=0.001$), and they reached the same carcass weight at an earlier age ($P=0.039$) compared to lambs born to control ewes⁽⁶⁴⁾. The intervention ewes displayed significantly higher 2-h postprandial glucose concentrations ($P<0.05$) compared to control ewes. It was concluded that transient high glycaemic intakes in the third trimester of pregnancy increased the birth weight of offspring and resulted in faster growth rate in early postnatal life. Sheep models are comparable to human models in studies of pregnancy and fetal development; thus, these findings support the results of the previous clinical studies in human models⁽⁶⁴⁾.

Findings from studies in gestational diabetic pregnancies have shown that consuming a high-CHO diet (>50% total daily energy) mainly composed of low-GI varieties can maintain blood glucose concentrations within normal ranges and is associated with a reduced incidence of fetal macrosomia. It is possible that maintenance of blood glucose levels within normal parameters in glucose-tolerant women or indeed women with upper levels of glucose below the diabetic range may have similar benefits on birth weight⁽⁶⁵⁾.

Conclusion

In summary, maternal blood glucose levels greatly influence fetal growth rate and subsequent size at birth, in both human and animal models. It is hypothesised that higher circulating concentrations of maternal blood glucose give rise to increased glucose transfer to the fetus, and the fetus responds by secreting more insulin. By maintaining maternal blood glucose levels within acceptable ranges during pregnancy, the incidence of fetal macrosomia and adverse pregnancy outcomes may be reduced. Results from the Hyperglycemia and Adverse Pregnancy Outcomes study showed that maternal hyperglycaemia less severe than that in overt DM is associated with adverse obstetric outcomes, and the present finding highlights the need to reassess our current standards for the diagnosis and treatment of hyperglycaemia in pregnancy⁽³⁶⁾. Longitudinal evidence revealed significant positive associations between postprandial blood glucose levels and measures of fetal adiposity⁽³⁷⁾. The loss in insulin sensitivity in mid-late pregnancy appears to be diet-induced, whereby dietary fibre and lower glycaemic intakes potentially have a protective effect⁽¹⁹⁾.

The GI may be particularly relevant for use in pregnancy. Previous studies have revealed that a low-GI diet can blunt the progressive increase in insulin resistance and increasing postprandial glucose levels seen in later pregnancy in women consuming a typical Western diet^(22,61–63). Altering the source of maternal dietary CHO may prove to be favourable in managing pregnancies with a history of

fetal macrosomia. Low-GI diets are associated with lower maternal glucose levels and lower infant birth weight, whereas high-GI diets are associated with higher maternal glucose levels, heavier birth weights and increased risk of LGA births. Fetal macrosomia increases the risk of adverse obstetric and neonatal outcomes^(8–11). Birth weight and ponderal index are predictors of adult obesity⁽⁶³⁾. Thus, giving low-GI dietary advice in early pregnancy may positively influence pregnancy outcomes⁽⁶⁶⁾. Despite positive findings in the literature, paucity still exists surrounding the impact of a low-GI diet in pregnancy. There are a limited number of studies published to date, many of which included relatively small numbers of subjects. Adequately powered controlled trials are warranted to further investigate the effects of the GI on maternal diet, maternal weight gain and pregnancy outcomes. Further research to assess the acceptability and sustainability of a low-GI diet in pregnancy is advocated, should it become standard dietary practice in pregnancy.

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