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Plenary Lecture

Maternal carbohydrate intake and pregnancy outcome

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Experimental evidence indicates that the primary maternal environmental factor that regulates feto–placental growth is substrate delivery to the placental site, which is the product of maternal substrate levels and the rate of placental-bed blood flow. Thus, maternal factors which change either substrate level or flow alter feto–placental growth rate. The best-studied substrate in human pregnancy is glucose, and there is a direct relationship between maternal blood glucose levels and size at birth. Altering the type of carbohydrate eaten (high- *v.* low-glycaemic sources) changes postprandial glucose and insulin responses in both pregnant and non-pregnant women, and a consistent change in the type of carbohydrate eaten during pregnancy influences both the rate of feto–placental growth and maternal weight gain. Eating primarily high-glycaemic carbohydrate results in feto–placental overgrowth and excessive maternal weight gain, while intake of low-glycaemic carbohydrate produces infants with birth weights between the 25th and the 50th percentile and normal maternal weight gain. The calculated difference in energy retention with similar total energy intakes is of the order of 80 000 kJ. Preliminary information from subsequent metabolic studies indicates that the mechanisms involved include changes in: daily digestible energy requirements (i.e. metabolic efficiency), substrate utilization (glucose oxidation *v.* lipid oxidation), and insulin resistance and sensitivity. Thus, altering the source of maternal dietary carbohydrate may prove to be a valuable tool in the management of pregnancies at risk for anomalous feto–placental growth and for the prevention and/or treatment of obesity and insulin resistance in the non-pregnant state.

Pregnancy: Diet: Glycaemic index: Metabolism: Feto–placental growth

At the outset, I want to make it clear that I am not a nutritionist and my knowledge in the area is limited. I am an obstetrician by training, and my research interests have always been the study of maternal–fetal interactions and how these interactions regulate feto–placental growth (Clapp, 1994). These interests inevitably led me to begin examining the feto–placental adaptive responses to everyday maternal behaviours such as physical activity and food intake. The latter is the topic of the present paper, which will begin with some background information about the role of environment in the regulation of fetal growth, followed by a brief review of the research findings which suggested that differences in maternal carbohydrate intake could alter feto–placental growth and maternal energy storage. Data addressing this point will then be presented, including some recent preliminary findings which identify at least some of the underlying regulatory mechanisms. Finally, there will be a broader discussion of the potential for using changes in carbohydrate intake as a public health tool to decrease the incidence of obesity and glucose intolerance in society at large.

Feto–placental growth regulation

A large body of experimental evidence indicates that the primary maternal extrauterine or 'environmental' factor which regulates feto–placental growth is substrate delivery to the placental site (the product of substrate level in the maternal compartment and the rate of placental-bed blood flow; Clapp, 1991, 1994). Factors which alter substrate

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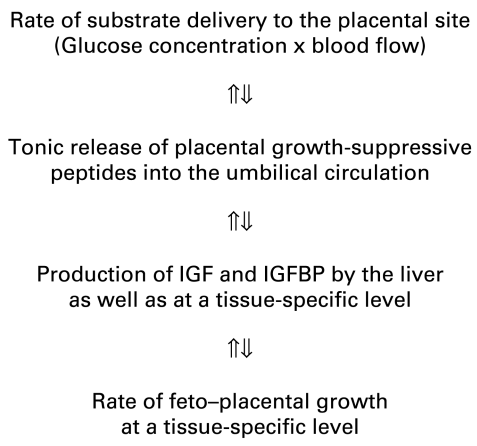

Fig. 1. A flow diagram outlining the nutritional mechanism for feto–placental growth regulation (for details, see p. 46). IGF, insulin-like growth factors; IGFBP, insulin-like growth factor-binding proteins.

delivery (either substrate levels or placental-bed blood flow) regulate the rate of feto–placental growth by initiating a change in synthesis and tonic release of placental growth-suppressive peptides into the fetal circulation. An overview of the regulatory mechanism is presented in Fig. 1 and reviewed in detail elsewhere (Clapp, 1991). Briefly, a fall in placental-bed blood flow and/or maternal substrate level increases the placental release of growth-suppressive peptides, which slow fetal growth rate by decreasing the expression of insulin-like growth factors and increasing their binding proteins in fetal tissues. On the other hand, a rise in flow and/or substrate levels decreases the placental release of growth-suppressive peptides, which increases fetal growth rate by increasing the expression of insulin-like growth factors and decreasing their binding proteins. This mechanism is sensitive, tissue specific, rapidly responsive and locally regulated. It explains why many maternal socio-demographic and lifestyle factors influence feto–placental growth and size at birth. For example, quiet standing in the workplace reduces both placental-bed blood flow and size at birth (Naeye & Peters, 1982), and severe reductions in maternal energy intake reduce maternal blood sugar levels, fetal growth rate and size at birth (Smith, 1947; Mellor, 1983), while a chronic increase in blood flow or maternal blood glucose levels increases size at birth (Langer *et al.* 1989*a*,*b*; Clapp *et al.* 2000*a*,*b*).

Recreational exercise and dietary carbohydrate

The path to the study of maternal carbohydrate intake as a regulator of feto–placental growth grew out of studies of maternal exercise. I became interested in maternal exercise during pregnancy about 20 years ago, a time when recreational exercise became a part of everyday life for many women in the USA. As exercise was known to reduce blood flow to the splanchnic bed, elevate body temperature and alter hormonal responses, there was concern that continuing regular exercise might increase reproductive risk in many areas (infertility, abortion, hypoxic brain damage, fetal growth restriction and premature labour; Metcalfe *et al.* 1984). These concerns stimulated studies which examined the effects of repetitive vigorous sustained maternal exercise throughout pregnancy on pregnancy outcome. Two of the major findings were that regular exercise was associated with an increase in placental growth and function (Clapp & Rizk, 1992; Jackson *et al.* 1995) and a decrease in birth weight primarily attributable to a decrease in fetal fat mass (Clapp & Capeless, 1990). Initially, these growth responses were felt to be entirely due to exercise-induced reductions in uterine blood flow and blood glucose levels intermittently limiting O_2 and substrate delivery to the placental site (Clapp & Capeless, 1991; Clapp *et al.* 2000*b*). Presumably the fall in O_2 tension stimulated placental overgrowth, while the decrease in glucose availability increased the placental release of growth-suppressive peptides into the fetal circulation, which selectively reduced growth of the fetal fat organ.

However, as our experience increased, we found that two women with virtually identical exercise performances and energy intakes occasionally experienced very different weight gains and were delivered of lean infants who differed in birth weight by more than 800 g. These large differences were clearly not the result of small differences in genetics or physical profile, and suggested that other variables were involved. As size at birth is clearly linked to maternal 24 h blood glucose levels (Mellor, 1983; Langer *et al.* 1989*a*,*b*), our search focused on factors other than exercise which might alter maternal blood glucose levels. During the early stages of the search I became acquainted with Mr Fraser and his provocative work (Fraser, 1981; Fraser *et al.* 1988) which indicated that unprocessed high-fibre carbohydrate sources in the diet lowered maternal blood glucose responses in late pregnancy. I also discovered, much to my surprise, that the blood sugar and insulin responses to many usual dietary carbohydrates were very different, and that carbohydrate sources were actually categorized by the magnitude of their induced glucose response using a comparative scale termed the glycaemic index (Wolever & Jenkins, 1986). Needless to say many of the 'aboriginal' high-fibre carbohydrate sources noted by Fraser (Fraser, 1981; Fraser *et al.* 1998) were low glycaemic.

This knowledge lead us to review the dietary information that had been gathered from the exercising women retrospectively. We found that women who reported eating primarily carbohydrates with a low-glycaemic index had gained less weight and had smaller babies than those who ate primarily high-glycaemic types of carbohydrate. This finding provided a logical answer to the observed differences in birth weight, but not to those in weight gain. That factor lead us to hypothesise that diet-induced differences in glucose and insulin levels have direct metabolic effects on energy balance via effects on alimentary absorption, BMR and/or energy substrate utilisation. This hypothesis led to a series of experiments which were designed to explore the issue in greater detail. Each series of experiments was approved by the Committee on Human Experimentation at MetroHealth Medical Center.

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Table 1. Typical low- and high-glycaemic-carbohydrate food sources

Low-glycaemic sources	High-glycaemic sources
Whole grains and unprocessed rice	Processed grains (flour, bread, cereals)
Beans and other non-tuberous vegetables	Tuberous vegetables (potato, carrot, parsnip)
Pasta (unless overcooked)	Typical desserts (baked goods, confectionery)
Most fruits and unsweetened juices	Soft drinks and sweetened juices
Unsweetened chocolate	Other snack foods
Nuts	Maize
Dairy products	Ripe bananas and some tropical fruit

Experimental results

First, palatable diets with exchanges containing either primarily high- or low-glycaemic types of carbohydrate were developed. Representative sources of both types of carbohydrate are listed in Table 1. The high-glycaemic sources rather than the low-glycaemic sources typify those prominent in the diets of individuals living in Western industrialized societies.

The first experimental series employed a cross-over design, non-pregnant volunteers and standardised mixed energy food challenges. The principal finding was that the 3 h postprandial glucose and insulin responses to 2260 kJ mixed meals containing 55% of their energy as high- or low-glycaemic carbohydrate were significantly higher ($P < 0{\cdot}001$) after ingesting the high-glycaemic meal (average 3 h glucose response 0·72 mmol/min *v.* 0·33 mmol/min, insulin response 168 nmol/min *v.* 102 nmol/min; Clapp, 1998).

The second experimental series employed a randomized prospective design in which all women were placed on a weight-maintaining diet containing primarily low-glycaemic types of carbohydrate before pregnancy and then, at 8 weeks gestation, they were randomized to continue the low-glycaemic diet or to change to an isoenergetic diet containing similar amounts and types of protein and fat, but high-glycaemic carbohydrate rather than low-glycaemic carbohydrate. The dietary intakes of all subjects were monitored twice weekly throughout the pregnancy, and maternal weight gain and the glucose and insulin responses to diet were assessed monthly (Clapp, 1998).

To date, ten women have completed each arm of the protocol. The women who were randomized to the high-glycaemic diet demonstrated a progressive increase in the area under the 3 h postprandial glucose and insulin responses throughout pregnancy, while those who consumed the low-glycaemic diet experienced no increase in their glucose response and a blunted insulin response. Average data for mid (24–28 weeks) and late (32–36 weeks) pregnancy are shown in Table 2. In Table 3 these data have been used to calculate several average indices of insulin resistance and sensitivity on the two diets (Matsuda & DeFronzo, 1999). Low-glycaemic forms of carbohydrate in the diet blunt the mid and late pregnancy increase in insulin resistance typically seen in women who live in Western industrialized societies.

The women who were randomized to the high-glycaemic diet also experienced excessive weight gain and were delivered of symmetrically larger infants and placentas (Clapp, 1997). The current morphometric data are presented in Table 4. The 800 g difference in birth weight is more than twice that mentioned earlier for vigorous sustained exercise, and the difference was due to an increase in both fat mass and lean body mass. Also, all morphometric variables were well within normal limits in the low-glycaemic diet group, while those in the high-glycaemic group exceeded the 90th percentile for the population under study (Amini *et al.* 1994).

These findings paved the way for detailed metabolic studies which are now being conducted at the Case Western University General Clinical Research Center at MetroHealth Medical Center. The subjects are non-pregnant women who are studied under controlled environmental and dietary conditions using a randomized cross-over design. Each woman is randomized to begin the protocol on either a high- or low-glycaemic weight-maintaining diet, and an energy balance study, multiple resting metabolic rates, a 16 h glucose and insulin profile and a euglycaemic clamp are completed during the third week. Then, after a wash-out period, the sequence is repeated on the other diet. To date the data indicate that there is no difference in resting metabolic rate, but the digestible energy intake necessary to maintain a stable weight is 8 % greater and total energy

Table 2. Glucose and insulin responses to a low-glycaemic or a high-glycaemic diet and a 2260 kJ test meal in mid (24–28 weeks) and late (32–36 weeks) pregnancy†
(Mean values with their standard errors)

	Low-glycaemic diet				High-glycaemic diet			
	Mid pregnancy		Late pregnancy		Mid pregnancy		Late pregnancy	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Fasting glucose (mmol/l)	3·83	0·11	3·78	0·11	4·00	0·17	4·28*	0·22
Fasting insulin (nmol/l)	67	9	63	9	83	11	131*	15
Average glucose increase postprandially (mmol/l per min)	0·61	0·18	0·60	0·23	1·44*	0·17	1·56*	0·22
Average insulin increase postprandially (nmol/l per min)	138	30	186	30	234*	36	324*	48

Mean values were significantly different from those for the low-glycaemic diet at the corresponding stage of pregnancy: *$P < 0{\cdot}05$.
†For details of experiment, see above.

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Table 3. Effects of a low-glycaemic diet *v.* a high-glycaemic diet on calculated insulin resistance and sensitivity in mid (24–28 weeks) and late (32–36 weeks) pregnancy†

	Low-glycaemic diet		High-glycaemic diet	
	Mid pregnancy	Late pregnancy	Mid pregnancy	Late pregnancy
Insulin resistance index‡	257	238	336*	565*
Insulin sensitivity index§	0·53	0·54	0·40*	0·24*
Whole-body insulin sensitivity index‖	24	19	10	6

Mean values were significantly different from those for the low-glycaemic diet at the corresponding stage of pregnancy: *$P < 0·05$.
†For details of experiment, see p. 47.
‡Fasting glucose concentration × fasting insulin concentration.
§405 ÷ (fasting glucose concentration × fasting insulin concentration).
‖10 000 divided by the square root of (fasting insulin × fasting glucose × the average increase in insulin × the average increase in glucose).

Table 4. Effect of a low-glycaemic diet *v.* a high-glycaemic diet on morphometric outcome variables of pregnancy†

	Low-glycaemic diet		High-glycaemic diet	
	Mean	SE	Mean	SE
Birth weight (kg)	3·33	0·11	4·17**	0·12
Crown–heel length (cm)	50·5	0·6	53·1**	0·5
Ponderal index‡	2·47	0·08	2·74**	0·04
Head circumference (cm)	34·5	0·3	36·6**	0·6
Fat mass (g)	266	44	427**	61
Lean body mass (kg)	3·06	0·09	3·74**	0·10
Placental growth (cm^3/week)	20	3	34**	3
Placental weight (g)	391	22	551**	42
Maternal weight gain (kg)	10·4	1·1	18·6**	1·1

Mean values were significantly different from those for the low-glycaemic diet: **$P < 0·01$.
†For details of experiment, see p. 47.
‡Weight × 100 ÷ crown–heel $length^3$.

intake is 14 % greater on the low-glycaemic diet. In addition, fasting and 16 h insulin levels are approximately 20 % lower and indices of insulin sensitivity are on average 18 % higher on the low-glycaemic diet. Finally, fat oxidation after a 12 h fast is 45 % higher on the low-glycaemic diet, while hepatic glucose production and oxidative glucose disposal are 11 and 28 % lower respectively.

Potential public health value of alterations in carbohydrate intake

These data strongly suggest the following points. First, that a large part of the normal variance in birth weight is related to differences in maternal dietary carbohydrate altering circulating maternal glucose and insulin levels. Dietary carbohydrates which elevate postprandial glucose levels in mid and late pregnancy markedly increase feto–placental growth rate, while those that maintain the glucose response to eating in the non-pregnant range result in an average rate of feto–placental growth. Thus, altering the source of maternal dietary carbohydrate may prove to be a valuable intervention in the prevention and/or management of pregnancies at risk for anomalous feto–placental growth. Randomized trials in women who have a history of a low-birth-weight outcome and/or those with a history of gestational diabetes in a previous pregnancy will be required to evaluate this possibility. Second, the type of carbohydrate eaten during pregnancy also influences maternal fat deposition and retention, probably by influencing both metabolic efficiency and insulin resistance and sensitivity. Third, the increased availability of high-glycaemic carbohydrate sources in Western industrialized societies may explain the gradual increase in both birth weight and pregnancy weight gain that has occurred over the last 50 years (Ziegler, 1976). Finally, the data strongly suggest that the metabolic differences in energy requirement, insulin sensitivity and substrate oxidation produced by altering the sources of dietary carbohydrate may be useful for the prevention and/or treatment of obesity and insulin resistance in the non-pregnant state.

Although controversial, the latter point has received a great deal of support in the recent literature (Smith, 1994; Morris & Zemel, 1999; Ludwig, 2000; Roberts, 2000). While the findings in young healthy active men are mixed (Keins & Richter, 1996; De Marco *et al.* 1999; Wee *et al.* 1999; Saltzman *et al.* 2001), the findings in children, women and men with pre-existing obesity and insulin resistance are encouraging (Frost *et al.* 1996, 1998; Jarvi *et al.* 1999; Meyer *et al.* 2000; Spieth *et al.* 2000; Agus *et al.* 2001). The findings of these investigators indicate that: obese children lose weight faster on a low-glycaemic diet; obese young men maintain a high level of resting energy expenditure and feelings of satiety during energy restriction on a low-glycaemic diet; insulin sensitivity is increased by introducing low-glycaemic carbohydrate into the diet of men and women with coronary artery disease and type 2 diabetes; epidemiological studies indicate that a low-glycaemic diet

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is associated with a lower incidence of type 2 diabetes in the elderly of both sexes. This information suggests that the response may be either magnified in, or limited to, individuals with some extent of pre-existing obesity or insulin resistance, which would help to explain the dramatic differences seen in mid and late pregnancy, a time of increasing insulin resistance in Western industrialized society. In any case, additional randomized well-controlled and monitored studies with well-defined outcome variables will be necessary to assess validity. If these results demonstrate real benefit, then introducing dietary recommendations stressing the health-related value of eating low-glycaemic types of carbohydrate into public health policy should be seriously considered.

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