

The Diamond Jubilee Summer Meeting of the Nutrition Society was held at the University of Sheffield on 10–12 July 2001

## Reproduction and Development Group Symposium on ‘Manipulating early diet’

### Nutrient insult in early pregnancy

Jane Coad<sup>1\*</sup>, Buthaina Al-Rasasi<sup>1</sup> and Jane Morgan<sup>2</sup>

<sup>1</sup>European Institute of Health and Medical Sciences and

<sup>2</sup>School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey GU2 7TE, UK

Nutrient insults in early pregnancy, such as nutrient deprivation during famines, are often associated with an unfavourable outcome. Suboptimal nutrition in the early stage of gestation has been linked to a number of adverse effects on fetal growth and development. Historically, nausea and vomiting in pregnancy (NVP) was an important contributor to pregnancy-related mortality; indeed, Charlotte Bronte died from starvation and dehydration after suffering very severe NVP 4 months into her first pregnancy (Gaskell, 1858). Although NVP seldom now progresses to be life-threatening, it affects the majority of pregnant women, and potentially presents a challenge to nutrient intake in the most vulnerable period of development. Symptoms range from mild (nausea only) to severe (a level of vomiting that restricts nutrient intake and ultimately threatens metabolic and electrolyte balance). Although NVP has been documented for thousands of years, its cause has not yet been satisfactorily elucidated, but seems to be related to endocrinological changes. Pregnant women also frequently report dietary cravings and aversions during pregnancy which can be linked to both the incidence and severity of NVP. Paradoxically, NVP appears to be positively associated with a favourable outcome of pregnancy, including increased birth weight and gestational age. The mechanisms by which NVP favours the outcome of pregnancy are not known. They may be related to women increasing their nutrient intake to alleviate symptoms, improving the quality of their diet or reducing energy expenditure. Alternatively, adaptation to a reduced nutrient intake might stimulate the expression of growth factors and affect placentation or metabolism, thus favouring fetal growth when NVP resolves.

#### Nausea and vomiting in pregnancy: Nutrient deprivation: Fetal development: Insulin-like growth factor: Maternal nutrition

##### Nausea and vomiting in pregnancy

Nausea and vomiting in pregnancy (NVP) affects 50–90% of pregnant women (Broussard & Richter, 1998). It usually presents as one of the first signs of pregnancy, within 2–4 weeks of fertilisation, peaks at the end of the first trimester and resolves by week 20 (Anderson, 1994). NVP is usually experienced as a complication of the first trimester of pregnancy, but a small proportion of women experience symptoms throughout pregnancy (Broussard & Richter, 1998). Although the onset of symptoms occurs typically in the morning, thus generating the term ‘morning sickness’, many women are affected episodically throughout the day

(Gadsby *et al.* 1993). Our retrospective study in Guildford (Al-Rasasi *et al.* 2001) shows that 72.6% of pregnant women reported experiencing NVP, which is similar to the incidence seen in other studies. In this group of women 12.3% suffered only in the morning, 7.5% only at night, whilst the remaining 80.2% of the group either experienced symptoms continuously or episodically through the day; so NVP is clearly a more suitable term than morning sickness.

NVP is usually classified as mild (nausea only), moderate (nausea and vomiting) or severe (where the extent of vomiting is so severe and prolonged that it can induce maternal weight loss, electrolyte imbalance and dehydration; hyperemesis gravidarum). In the group of women

**Abbreviations:** hCG, human chorionic gonadotrophin; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; NVP, nausea and vomiting in pregnancy.

\*Corresponding author: Jane Coad, present address Institute of Food, Nutrition and Human Health, Massey University, Private Bag 11222, Palmerston North, New Zealand, fax +64 6350 5671, email j.coad@massey.ac.nz

we studied, 57.5% could be classified as experiencing mild NVP, 37% moderate and 5.5% severe, including 1.4% diagnosed with hyperemesis gravidarum and hospitalised. However, within each of these classifications a range of symptoms resulting in quite different effects on dietary intakes might be experienced. For instance, a woman who experienced vomiting might only be affected at a certain period of the day, and although the NVP would be classified as moderate, her daily nutrient intake might have been less affected than that of a woman who experienced mild NVP continuously through the day.

NVP has been positively associated with a number of maternal characteristics. These characteristics include primiparity, younger maternal age and low educational achievement (Klebanoff *et al.* 1985), multiple gestation and intolerance of oral contraceptives (Jarnfelt-Samsioe *et al.* 1983), high maternal BMI (Klebanoff *et al.* 1985), high placental weight, non-smoking, family history and history of NVP in previous pregnancies (Gadsby *et al.* 1997). It is reported more often in Westernised countries (Broussard & Richter, 1998) and is associated with poorer diets, irregular eating patterns and stressful pregnancies (Iatrakis *et al.* 1988). Women who report their occupation as housewife have also been found to have an increased incidence of NVP compared with those who are in paid employment (Weigel & Weigel, 1988).

Although NVP has been recorded as a complication of pregnancy for over 4000 years (Fairweather, 1968), surprisingly little is known about its aetiology. Frustratingly, for many years most obstetricians attributed psychological factors, particularly negative personal relationships or undesired pregnancies, as the prime causes of NVP (Semmens, 1971). Now we know that a number of physiological factors are implicated. The symptoms of NVP follow a time-course that mirrors the secretion of placental human chorionic gonadotrophin (hCG; Soules *et al.* 1980), but there are no consistent patterns in levels of hCG and severity or duration of symptoms. Both oestrogen and progesterone levels increase during pregnancy. An increased sensitivity to oestrogen is implicated because women who report intolerable levels of nausea with oral contraceptives have a higher incidence of NVP (Jarnfelt-Samsioe *et al.* 1983). Both overweight women and those who do not smoke have elevated oestrogen levels and a higher incidence of NVP (Depue *et al.* 1987). However, again there is no correlation between hormone levels and symptoms.

The relationship between NVP and progesterone is related to the effects that progesterone has on smooth muscle tone of the gut that results in gastric hypotonicity, hyposecretion and hypoperistalsis, all of which promote gastric wave dysrhythmia and delayed gastric emptying. The increased progesterone levels of pregnancy reduce the patency of the lower oesophageal sphincter, thus increasing gastric reflux and affecting motility and emptying of the stomach. It has been found that protein-rich test meals (i.e. protein energy ratio (proportion of energy from protein) > 53%), which seem to lessen symptoms of NVP, reduce gastric slow wave dysmotility (Jednak *et al.* 1999); however, this finding has been contested by Maes *et al.* (1999) who found that gastric emptying of solids was not significantly delayed in pregnant women.

The severity of symptoms of NVP has also been linked to altered thyroid function (Mori *et al.* 1988); a decrease in thyroid-stimulating hormone and an increase in thyroxine were measured. This change may occur because hCG, which has some structural similarities with thyroid-stimulating hormone, acts as a thyroid-stimulating factor. However, hyperthyroidism *per se* is not associated with nausea and vomiting outside pregnancy.

Other suggested causes of NVP include unidentified nutrient deficiency, vitamin B<sub>6</sub> deficiency (Emelianova *et al.* 1999), high prepregnancy intake of saturated fat (Signorello *et al.* 1998) and a pattern of food aversions before pregnancy (Crystal *et al.* 1999).

### The effects of nutrient deprivation in early pregnancy

A woman's reproductive capability is highly susceptible to nutrient insult or deficiencies during the period of ovum maturation and early embryonic development. During the Dutch Hunger Winter there was an increase in perinatal mortality and congenital abnormality in pregnancies where women were exposed to the famine early in gestation (Stein *et al.* 1975). Work from the Borough of Hackney in East London (Doyle *et al.* 1990) has provided convincing evidence of an association between maternal nutritional status and birth outcome, which can only have had its origin in early pregnancy. In these studies women are also likely to have been poorly nourished both before conception and throughout pregnancy rather than only in the early stages of gestation.

The early *in utero* period of growth and development of the human fetus represents a period of rapid cell division, occurring at different times in different tissues, resulting in the concept of fetal programming. During these critical periods of selective tissue growth, the nutritional and hormonal environment may exert influences on the underlying programmed changes, resulting in reduction in cell numbers, changes in the distribution of cell type and in the resetting of hormonal feedback (Godfrey & Robinson, 1998). The current evidence suggests that, although the fetal genome determines growth potential *in utero*, it plays only a minor role in the determination of growth that is actually achieved, although little is understood about the maternal influences (including nutrition) which programme the growth and development of the human fetus. The concept of fetal programming has important implications, because it is now well established that variations in fetal size and body proportions at birth have important connotations in terms of health outcomes and pathological changes in adult life.

The potential effect of different planes of maternal nutrition at different stages of pregnancy and the subsequent influence on the growth of the fetus is a complex subject. Barker (1995) hypothesised that undernutrition in early gestation would lead to a proportionately small baby predisposed to hypertension and haemorrhagic stroke, but not CHD, in adulthood. Lumey (1998a) contested this hypothesis after analysing data from the Dutch Hunger Winter and finding little effect on birth weight after undernutrition in the first and second trimester. There is compelling evidence from the Dutch Famine studies, when food availability was progressively reduced to < 5400 kJ/d

**Table 1.** Mean birth weight (adjusted for gender; g) in 538 pregnancies according to the mother's daily intake of carbohydrate in early pregnancy and meat protein intake in late pregnancy (intakes calculated by food-frequency questionnaire; Godfrey *et al.* 1996)

Meat-protein intake (g/d)*	Carbohydrate intake (g/d)†			
	<265	265–340	>340	All
<23.5	3450	3419	3321	3405
23.5–34.0	3539	3472	3359	3451
>34.0	3529	3443	3443	3468
All	3501	3444	3381	3442

\* Birth weight fell by 3.1 g for each 1 g decrease in meat-protein intake in late pregnancy.

† Birth weight fell by 165 g ( $P < 0.005$ ) for each log 1 g increase in carbohydrate intake in early pregnancy.

by April 1945, that exposure to famine in the first trimester of pregnancy had irreversible effects on the offspring which have become evident in adulthood (Stein *et al.* 1975). The effects of maternal undernutrition in early gestation include higher levels of obesity (Ravelli *et al.* 1999), more atherogenic lipid profiles and increased prevalence of CHD (Roseboom *et al.* 2000a), and altered hepatic function (Roseboom *et al.* 2000b) in adulthood. Interestingly, from a parallel study, there is evidence of compensatory placental growth after famine exposure in the first trimester of pregnancy (Lumey 1998b). It has been argued, however, that these historical observations do not represent the norm, and that thinness at birth is a result of suppressed placental development early in pregnancy (Godfrey *et al.* 1997).

More recent evidence of the influence of maternal nutrition in pregnancy in relation to placental and fetal growth has suggested that birth weight and the placental ratio (placental weight:birth weight) are affected early in gestation (Godfrey *et al.* 1996; see Table 1).

Women who consumed higher than normal amounts of food in early pregnancy (expressed by carbohydrate intake) had small placentas and infants with lower birth weights, especially if combined with low intakes of animal protein in late pregnancy (Godfrey *et al.* 1996). However, long-term effects following suboptimal nutrition in early gestation may result in altered body proportions or even occur in the absence of an effect observable at birth. Mild maternal dietary impairment in sheep demonstrates that when fetal and compensatory mechanisms are adequate, so that birth weight is not reduced, fetal cardiovascular development is altered (Hawkins *et al.* 2000). The effects of undernutrition in early pregnancy probably depend on both the magnitude of the deprivation and nutritional state before and afterwards.

It may seem paradoxical, therefore, that although NVP apparently presents a nutritional challenge early in pregnancy, a number of studies have reported that NVP in the first half of pregnancy is associated with a favourable outcome. The risks of miscarriage (Weigel & Weigel, 1989), perinatal death, low birth weight and premature delivery (Tierson *et al.* 1986) and congenital heart defects (Boneva *et al.* 1999) are all reduced in women who experience NVP. However, very severe NVP or hyper-

emesis gravidarum, especially if associated with loss of prepregnancy weight, has been associated with less favourable outcomes (Tsang *et al.* 1996).

Although NVP is associated with a favourable outcome of pregnancy, it frequently has negative effects on quality of life during the pregnancy. It causes discomfort and is associated with irritability and tiredness, which may affect social and economic functioning, particularly employment.

### Possible mechanisms

One possible mechanism by which NVP is associated with a favourable outcome of pregnancy is that despite causing discomfort and distress associated with food, NVP may not result in reduced nutrient intake, but may actually increase it or alter the macronutrient profile to favour the consumption of certain nutrients. We have found that some women (31%) reported that their symptoms were alleviated by continually snacking, usually on carbohydrate-rich foods. Another possibility is that NVP stimulates a change in physical behaviour so that women change their level of activity, and hence energy expenditure will alter the balance in favour of maternal and fetal tissue growth.

Alternatively, quality of diet might be altered. Our studies have found a strong association between symptoms of NVP and reported dietary cravings and aversions (Al-Rasasi *et al.* 2001). Women reported experiencing cravings, particularly for fruit and sweet-tasting foods, dairy products and protein-rich foods, whereas the most commonly reported aversions were for drinks containing caffeine, strong tasting and smelling foods and fatty or greasy foods. These cravings and aversions may be linked to altered taste perceptions in pregnancy. Indeed, it has been shown that there are differences in bitter-taste perception in women with a history of severe vomiting during pregnancy (Sipiora *et al.* 2000).

Deutsch (cited in Flaxman & Sherman, 2000) proposed that NVP had evolved as a method of communication which alerted the pregnant woman's partner and kin to her pregnancy. Although it was suggested that NVP might discourage intercourse or signal impending need for additional food or protection, it may simply constantly remind the woman of her own pregnancy and induce her to change behaviour. Women do appear to positively change their diet in pregnancy in response to public health messages (Anderson, 2001).

Another intriguing explanation may be that NVP, which coincides with the most sensitive periods of embryonic organogenesis, protects the developing embryo by causing women to reject or avoid foods containing potentially-harmful teratogens or abortifacients (Hook, 1980; Profet, 1988). Foods implicated include strong-tasting vegetables, beverages containing alcohol and caffeine, and meat, fish, poultry and eggs. This 'Stone Age theory' has been strongly contested by Brown *et al.* (1997). However, Flaxman & Sherman (2000) investigated the concept further and hypothesised that NVP causes women to avoid foods that are more likely to be contaminated with parasites and pathogens at a time when pregnancy causes immunosuppression, leaving women more vulnerable to infection. This concept was supported by the findings that societies (e.g. Bhil, Mbundu, Omaha, Papago, Siriono, Tarahumara and Woleai)

where NVP had never been observed were more likely to have only plants as their dietary staple. Flaxman & Sherman (2000) analysed the results of twenty studies and found that the most common aversions were to meat and non-alcoholic beverages.

### Placental development

Much of what we know about the effects of maternal nutrition on fetal and placental growth and development is based on animal models. In experimental animals effects of undernutrition on placental weight are particularly variable (Harding & Johnston, 1995). Fetal and placental responses to undernutrition in ewes depend on the magnitude, timing and duration of nutrient restriction (Symonds *et al.* 2001). Maternal nutrient restriction in ewes in early gestation tends to increase placental weight at term. In early gestation, during the period of rapid placental growth, maternal nutrient restriction initially restricts placental growth (Clarke *et al.* 1998), but when the mother is subsequently fed to requirements the placental size increases and fetal growth is restored (Heasman *et al.* 1999). These experiments performed in sheep have demonstrated that severe undernutrition reduces placental mass, but lesser reductions in maternal intake have the opposite effect (Robinson *et al.* 1995; Gadd *et al.* 2000). In contrast to the discoid structure of the human placenta, sheep have cotyledonary placentas in which villus contact is established in a number (forty to 100) of small areas called placentomes. Each placentome is formed by the projection of interdigitating fetal villi into specialised predetermined regions of the maternal stroma called caruncles. In the nutrient-restricted group of sheep both placental weight and the number of placentomes were significantly increased ( $P < 0.05$ ; Heasman *et al.* 1999). The practice of 'flushing' in sheep husbandry, in which sheep are transferred from good pasture to poorer pasture just for the early period of gestation, appears to promote fetal growth by stimulating placental development (McCrabb *et al.* 1992).

Other studies have shown that overfeeding adolescent (still growing) sheep early in gestation promotes rapid maternal growth, but results in a restriction of placental mass and a significant ( $P < 0.001$ ) decrease in birth weight which is related to nutritional status rather than gynaecological immaturity (Wallace, 2000). In these over-nourished adolescent sheep an altered maternal hormonal profile apparently promoted maternal tissue anabolism at the expense of fetal growth (Wallace *et al.* 1997). In contrast, adolescent ewes fed moderately during the first trimester had significantly higher fetal cotyledon numbers than those fed on a higher nutritional plane ( $P < 0.007$ ; Wallace *et al.* 1999). From studies in sheep, it seems that the placenta undergoes an adaptive compensatory response to mild maternal undernutrition during this period of rapid placental growth, thus optimising transplacental exchange efficiency. It is possible that NVP is associated with a favourable outcome of pregnancy because maternal nutrient restriction early in gestation favours placental development. Can we extrapolate these findings to man?

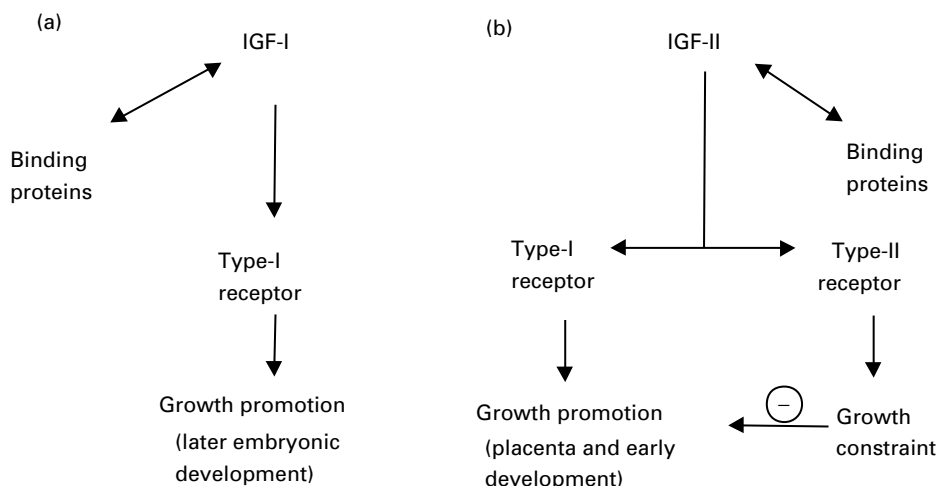
### The insulin-like growth factor axis

The mechanisms by which maternal nutrient intake affect fetal and placental growth seem to be mediated by the insulin-like growth factor (IGF) axis. The IGF are low-molecular-weight polypeptides (7 kDa), with structural homology to proinsulin, which promote mitosis and differentiation. They play an important role in determining fetal and placental growth (van Kleffens *et al.* 1998). The IGF and their binding proteins (IGFBP), which are produced by the placenta, act as autocrine or paracrine factors at or close to their site of synthesis. Several components of the IGF system, including IGF and IGFBP, have been demonstrated to be affected by nutrition. The six homologous IGFBP have high binding affinity for IGF-I and IGF-II (Baxter, 2000) which may be altered by modification of IGFBP such as phosphorylation and proteolysis. Binding of IGF to IGFBP can result in either inhibition or enhancement of IGF action. The actions of IGF-I and IGF-II are influenced both by levels of the specific IGFBP and by the expression of IGF receptors on the target tissues. Studies using different types of knockout mice have led to the identification of the roles of various components of the IGF axis and their effects on fetal growth *in utero*.

Both maternal and fetal IGF-I levels affect fetal growth rate (Gluckman, 1995). IGF-I predominantly influences growth in late gestation and postnatally, whereas IGF-II has a stronger influence on embryonic growth in early development (Fig. 1). Both human fetal and neonatal size correlate with circulating IGF-I concentrations in cord blood at term (Gluckman, 1995), and IGF-I levels are sensitive to maternal nutrient intake. Placental glucose transfer controls fetal insulin release, which regulates IGF-I release and, therefore, fetal growth; IGF-I also affects placental metabolism and controls placental substrate delivery to the fetus. There is a switch during development from IGF-II to IGF-I, but the actions of both IGF on fetal growth are primarily mediated by the type-1 receptor (Gluckman & Harding, 1997). IGF-II seems to require much greater changes in nutritional and hormonal factors than IGF-I before plasma and tissue levels are affected (Straus & Takemoto, 1990). This situation means that in early development, when IGF-II is the dominant growth factor, the fetus is less sensitive to environmental influences such as nutrient deprivation. Later in gestation maternal fasting causes a decrease in IGF-I and increases fetal liver expression of IGFBP-1, which contributes to fetal growth retardation (Straus *et al.* 1991). Thus, when IGF-I is the predominant influence the fetus responds to nutrient deprivation by promptly decreasing growth rate.

All six IGFBP are produced by human decidualised endometrium. IGFBP-1 is the main secretory product of the human decidualised endometrium and is the predominant IGFBP in the amniotic fluid and fetal plasma (Drop *et al.* 1984). Concentrations of IGFBP-1 increase during the first trimester and plateau at mid-gestation, and are higher in intrauterine growth retardation (Giudice *et al.* 1997). Both IGF-I and IGF-II regulate IGFBP-1 in a biphasic manner; low concentrations stimulate IGFBP-1, while high concentrations are inhibitory (Westwood, 1999). Production of





**Fig. 1.** The insulin-like growth factor (IGF) axis mediates the effects of nutrition on growth. (a) The activity of IGF-I is moderated by the six IGF-binding proteins; binding can either inhibit or enhance activity. IGF-I regulates growth via the type-1 receptor predominantly in the latter part of gestation. (b) IGF-II promotes growth in early gestation via the type-1 receptor; its activity is also moderated by binding proteins. However, affinity of paternally-expressed IGF-II for the type-2 receptor is higher than that for the type-1 receptor. Binding to the maternally-expressed type-2 receptor limits the amount of IGF-II available to interact with the type-1 receptor, and so effectively constrains growth.

IGFBP-1 is inhibited by insulin and stimulated by progesterone and relaxin. The affinity of IGFBP-1 is affected by its phosphorylation state; phosphorylated IGFBP-1 has a higher affinity for IGF-I and so can inhibit IGF-I activity (Westwood, 1999). The IGFBP are affected by nutritional state to different extents; IGFBP-1 is regulated acutely by nutrient intake, with high levels in the fasted state and rapid postprandial decreases. IGFBP-3 is relatively stable, but is depressed after prolonged periods of severe malnutrition, and IGFBP-2 is highly dependent on dietary protein intake (Ketelslegers *et al.* 1996).

The effects of the IGF are mediated via two specific receptors, type-1 and type-2, which are expressed in high density on most fetal and placental cells. The type-1 and type-2 receptors co-localise with IGF-II, which suggests the receptors compete for IGF-II (Zhou & Bondy, 1992). IGF-II interacts with type-1 and type-2 IGF receptors; the type-2 receptor binds IGF-II with high affinity and IGF-I with an affinity about 100-fold lower (Han & Carter, 2000). While the type-1 receptor promotes growth, the competitive non-signalling type-2 receptor limits growth (Czech, 1989); it is also implicated in IGF-II degradation (O'Dell & Day, 1998). A soluble circulating form of the type-2 receptor inhibits IGF-II-mediated DNA synthesis and therefore probably constrains fetal growth (Ong *et al.* 2000). Size at birth correlates with circulating IGF-II:soluble type-2 receptor levels (Ong *et al.* 2000).

It has been suggested by Haig & Graham (1991) that, as the gene for the type-2 receptor is maternally imprinted and IGF-II is paternally imprinted (DeChiara *et al.* 1991), this situation presents an example of genetic conflict. Paternal genome expression promotes growth via the expression of IGF-II, but the maternally-expressed type-2 receptor can act to mop up IGF-II, preventing it from binding to the growth-promoting type-1 receptor. Thus, an excess of type-2 receptor expression will limit growth of placenta and,

therefore, constrain fetal growth, thus limiting the metabolic demands placed on the mother.

### Nutrient regulation of growth

The preimplantation embryo bathes in fluid that is rich in IGF and IGFBP (van Kleffens *et al.* 1998). The IGF-II gene is expressed early after fertilisation and has been demonstrated in the two-cell-stage embryo (Heyner *et al.* 1989). Fetal tissues overexpress IGF-II compared with postnatal tissues. Successful implantation, placental development and fetal growth depend on migration of the IGF-II-producing trophoblast into the maternal decidua (Minniti *et al.* 1992). IGF-II is produced in abundance by the trophoblast cells of the placenta (van Kleffens *et al.* 1998), and is particularly prevalent in sites of cell differentiation; its concentration is highest in the trophoblastic columns of anchoring villi, especially at the leading edge, implying it plays a pivotal role in trophoblastic invasion (Westwood, 1999). The maternal decidua and uterine vessels express IGFBP-1, which is involved in orchestrating trophoblast migration (Westwood, 1999). This interaction between IGF-II from the cytotrophoblast and decidua IGFBP at the maternal-fetal interface of the primate placenta is thought to be critical during trophoblastic invasion and decidualisation (Han & Carter, 2000). IGFBP-2 is not detectable early in gestation (Reynolds *et al.* 1997). There appears to be a functional relationship between IGF-II and IGFBP-2; during the early invasive period when the placenta is establishing, IGF-II expression is high and unopposed by IGFBP-2, whereas later in gestation the ratio is reversed (Zhou & Bondy, 1992).

IGF-II-knockout mice have significant growth retardation, especially in the early stages of gestation; IGF-II gene disruption is associated with severe placental growth retardation (DeChiara *et al.* 1990). IGF-II appears to be

involved in the regulation of body composition in the mouse; it controls fluid uptake by direct action on the maternal capillaries (Gardner *et al.* 1999), increasing vascular endothelial growth factor, which increases capillary permeability and promotes angiogenesis. Vascular endothelial growth factor increases NO production, which is positively correlated with birth weight and placental weight (Hata *et al.* 1998). Other processes mediated by IGF-II are thought to include increased cell mass (Zaina & Squire, 1998) and cell survival (Christofori *et al.* 1994) and rate of progression through the cell cycle (Eggenschwiler *et al.* 1998). IGF-II also regulates the cell number in the placenta and plays a role in the differentiation of placental glycogen-producing cells (Lopez *et al.* 1996).

In summary, the mechanism by which NVP is associated with a favourable outcome of pregnancy, particularly increased birth weight, may be mediated through adaptation to reduced nutrient intake in early gestation, favouring compensatory placental development, which subsequently optimises fetal development. During the early stages of development, when trophoblastic invasion is occurring and the placenta is establishing, the predominant growth factor involved in promoting growth via the type-1 receptor is IGF-II, which is fairly resistant to fluctuations in maternal nutrient intake, thus placental growth is maintained. At this time IGFBP-2 is not detectable in the fetal circulation, thus potential competition with the type-1 receptor is minimal.

It is necessary to be cautious when drawing conclusions from mechanisms elucidated in different species. The structures of the primate discoid placenta and the cotyledonous placenta of ruminants are very different. None of the species studied share identical expressions of IGF and IGFBP. Also placental weight *per se* is a gross measurement; weight alone does not necessarily indicate placental efficiency of nutrient transfer, which is likely to be affected more by depth of insertion or differential expression of transport mechanisms rather than by weight.

### Nausea and vomiting in pregnancy

An alternative explanation of the mechanisms is that NVP affects nutrient partitioning via altered metabolism. During the first half of pregnancy increased sensitivity to insulin promotes maternal anabolism. Subsequently, in the latter part of pregnancy increasing insulin resistance stimulates maternal catabolism and maintains higher substrate levels, favouring placental transport when fetal growth is high. Altering intake in early gestation could moderate the extent of deposition of maternal stores.

A high nutritional intake in adolescent sheep early in gestation resulted in suppressed placental and fetal growth (Wallace *et al.* 1997). This phenomenon was suggested to be mediated by elevated insulin levels and maternal IGF-I, which promoted maternal tissue deposition in early gestation at the expense of placental development and caused down regulation of placental IGF-I levels. It has been hypothesised that, by causing reduced energy intake in early gestation, NVP would lower maternal insulin and IGF-I levels, thus abrogating the anabolic drive and ensuring that nutrient partitioning favoured placental, and ultimately fetal, growth (Huxley, 2000). As insulin potentially inhibits hCG

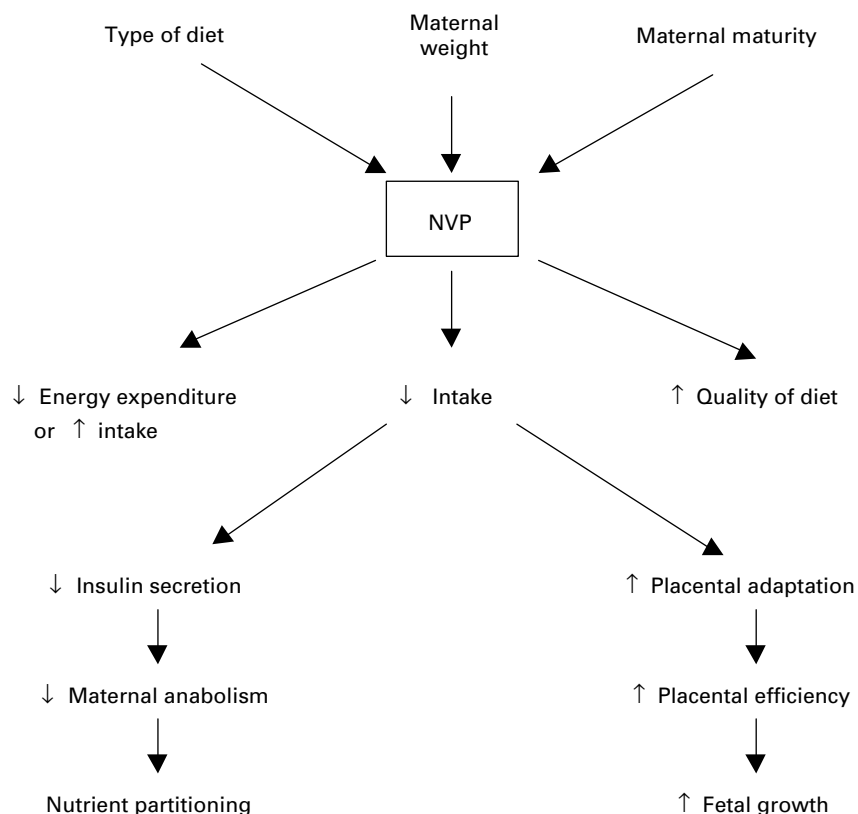
production (Barnea *et al.* 1993), reducing maternal insulin levels would optimise hCG production and subsequent effects of thyroxine on placental development. Huxley (2000) also suggests that the positive effect of NVP on placental development could be potentially augmented by placental leptin suppressing appetite. Placental production of leptin peaks in the first trimester (Masuzaki *et al.* 1997); thus, it could either augment the effect of NVP or provide an alternative mechanism for suppressing maternal energy intake during placental development. Maternal leptin concentration is negatively correlated with placental size (Schubring *et al.* 1997). Maternal dietary intake is also inversely related to peripheral progesterone concentration, so that a lower nutrient intake in early gestation facilitates progesterone production, which has positive effects on growth of the embryonic inner cell mass (Wallace, 2000).

### Summary

Although mild-to-moderate NVP is associated with a positive outcome of pregnancy, favouring both fetal growth and gestational length, this positive effect depends on nutritional status before conception and after the symptoms of NVP have resolved. Providing a woman enters pregnancy with adequate nutrient stores, the fetal growth trajectory will be set optimally and there will be less competition between maternal nutrient requirements and those of the developing conceptus. Indeed, it has been suggested that women of below normal body weight are likely to experience NVP to a lesser extent (Huxley, 2000). Certainly, women who are less well nourished before and during conception tend to gain more weight during the course of pregnancy and to produce lighter babies (Doyle *et al.* 1990). Similarly, adolescent women, who presumably have a stronger anabolic drive, also have a poorer outcome of pregnancy (Scholl *et al.* 1995) in a similar pattern to that of pregnant adolescent sheep (Wallace, 2000).

The other requirement for enhanced fetal development is that dietary intake is adequate to match the transfer capacity of the placenta after symptoms of NVP have abated, during which time fetal growth is constrained by nutrient availability in the second half of pregnancy (Bauer *et al.* 1998). At this time in gestation IGF-I takes over as the predominant promoter of fetal growth and stimulates maturation of fetal organs. Optimal early development of the placenta could affect subsequent levels of hormones, growth factors and transporter proteins which are produced later to control distribution of substrates and regulate fetal growth. As well as IGF-I, glucose-transporter proteins (Illsley, 2000), placental growth hormone (Alsati *et al.* 1998) and placental lactogen (O'Dell & Day, 1998) have been shown to be important in regulating both placental substrate availability and uptake, and maternal appetite and metabolism.

As well as causing decreased nutrient intake which may affect either placental development or nutrient partitioning, NVP results in an increased nutrient intake in some women (Fig. 2). It can be hypothesised that this situation may be related to rates of maternal growth before conception. NVP can also potentially result in dietary changes either by the effects of changing intake on severity of symptoms, or because it acts to continuously remind the woman she is



**Fig. 2.** Maternal diet, size and maturity affect the severity of nausea and vomiting in pregnancy (NVP). The mechanisms by which NVP is positively associated with the outcome of pregnancy could include (1) increasing (↑) intake or decreasing (↓) energy expenditure, (2) reducing intake, which could either alter maternal metabolism and nutrient partitioning in favour of the conceptus and/or stimulate placental adaptation and/or (3) altering the quality of the diet.

pregnant. NVP, or the advice that is given to women who experience it, may result in an altered diet. Elucidating the mechanisms by which NVP has a positive effect on birth weight will help to identify what nutritional advice is appropriate.

### Acknowledgements

B.A.-R. is in receipt of a University of Surrey Research scholarship that we gratefully acknowledge. We thank Dr John Nicholls for his support and helpful discussions.

### References

- Al-Rasasi B, Siegler R, Nichols J, Coad J & Morgan J (2001) Dietary cravings and aversions in pregnancy. *Proceedings of the Nutrition Society* **60**, 136A.
- Alsat E, Guibourdenche J, Couturier A & Evain-Brion D (1998) Physiological role of human placental growth hormone. *Molecular and Cellular Endocrinology* **140**, 121–127.
- Anderson AS (1994) Managing pregnancy sickness and hyperemesis gravidarum. *Professional Care of Mother and Child* **4**, 13–15.
- Anderson AS (2001) Pregnancy as a time for dietary change. *Proceedings of the Nutrition Society* **60**, 497–504.
- Barker DJ (1995) Fetal origins of coronary heart disease. *British Medical Journal* **311**, 171–174.
- Barnea ER, Neubrun D & Shurtz-Swirski R (1993) Effect of insulin on human chorionic gonadotrophin secretion by placental explants. *Human Reproduction* **8**, 858–862.
- Bauer MK, Harding JE, Bassett NS, Breier BH, Oliver MH, Gallaher BH, Evans PC, Woodall SM & Gluckman PD (1998) Fetal growth and placental function. *Molecular and Cellular Endocrinology* **140**, 115–120.
- Baxter RC (2000) Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities. *American Journal of Physiology* **278**, E967–E976.
- Boneva RS, Moore CA, Botto L, Wong LY & Erickson JD (1999) Nausea during pregnancy and congenital heart defects: a population-based case-control study. *American Journal of Epidemiology* **149**, 717–725.
- Broussard CN & Richter JE (1998) Nausea and vomiting of pregnancy. *Gastroenterology Clinics of North America* **27**, 123–151.
- Brown JE, Kahn ES & Hartman TJ (1997) Profet, profits, and proof: do nausea and vomiting of early pregnancy protect women from 'harmful' vegetables? *American Journal of Obstetrics and Gynecology* **176**, 179–181.
- Christofori G, Naik P & Hanahan D (1994) A second signal supplied by insulin-like growth factor II in oncogene-induced tumorigenesis. *Nature* **369**, 414–417.
- Clarke L, Heasman L, Juniper DT & Symonds ME (1998) Maternal nutrition in early–mid gestation and placental size in sheep. *British Journal of Nutrition* **79**, 359–364.
- Crystal SR, Bowen DJ & Bernstein IL (1999) Morning sickness and salt intake, food cravings, and food aversions. *Physiology and Behavior* **67**, 181–187.

- Czech MP (1989) Signal transmission by the insulin-like growth factors. *Cell* **59**, 235–238.
- DeChiara TM, Efstratiadis A & Robertson EJ (1990) A growth deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. *Nature* **345**, 78–80.
- DeChiara TM, Robertson EJ & Efstratiadis A (1991) Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* **64**, 849–859.
- Depue RH, Bernstein L, Ross RK, Judd HL & Henderson BE (1987) Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *American Journal of Obstetrics and Gynecology* **156**, 1137–1141.
- Doyle W, Crawford MA, Wynn AHA & Wynn SW (1990) The association between maternal diet and birth dimensions. *Journal of Nutritional Medicine* **1**, 9–17.
- Drop SL, Kortleve DJ, Guyda HJ & Posner BI (1984) Immunoassay of a somatomedin-binding protein from human amniotic fluid: levels in fetal, neonatal, and adult sera. *Journal of Clinical Endocrinology and Metabolism* **59**, 908–915.
- Eggenchwiler J, Ludwig T, Fisher P, Leighton PA, Tilghman SM & Efstratiadis A (1998) Mouse mutant embryos overexpressing IGF-II exhibit features of the Beckwith-Wiedemann and the Simpson-Golabi-Behmel syndrome. *Genes and Development* **11**, 3128–3142.
- Emelianova S, Mazzotta P, Einarson A & Koren G (1999) Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. *Clinical and Investigative Medicine* **22**, 106–110.
- Fairweather DVI (1968) Nausea and vomiting in pregnancy. *American Journal of Obstetrics and Gynecology* **102**, 135–175.
- Flaxman SM & Sherman PW (2000) Morning sickness: a mechanism for protecting mother and embryo. *Quarterly Review of Biology* **75**, 113–148.
- Gadd TS, Aitken RP, Wallace JM & Wathes DC (2000) Effect of a high maternal dietary intake during mid-gestation on components of the utero-placental insulin-like growth factor (IGF) system in adolescent sheep with retarded placental development. *Journal of Reproduction and Fertility* **118**, 407–416.
- Gadsby R, Barnie-Adshead AM & Jagger C (1993) A prospective study of nausea and vomiting during pregnancy. *British Journal of General Practice* **43**, 245–248.
- Gadsby R, Barnie-Adshead AM & Jagger C (1997) Pregnancy nausea related to women's obstetric and personal histories. *Gynecologic and Obstetric Investigation* **43**, 108–111.
- Gardner RL, Squire S, Zaina S, Hills S & Graham CF (1999) Insulin-like growth factor-2 regulation of conceptus composition: effects of the trophoblast and inner cell mass genotypes in the mouse. *Biology of Reproduction* **60**, 190–195.
- Gaskell EC (1858) *The Life of Charlotte Bronte*. Oxford: Oxford University Press.
- Giudice LC, Martina NA, Crystal RA, Tazuke S & Druzin M (1997) Insulin-like growth factor binding protein 1 at the maternal-fetal interface and insulin-like growth factor I, insulin-like growth factor II, and insulin-like growth factor binding protein 1 in the circulation of women with severe preeclampsia. *American Journal of Obstetrics and Gynecology* **176**, 751–757.
- Godfrey K, Barker DJP, Robinson S & Osmond C (1997) Maternal birthweight and diet in pregnancy in relation to the infant's thinness at birth. *British Journal of Obstetrics and Gynaecology* **104**, 663–667.
- Godfrey K & Robinson S (1998) Maternal nutrition, placental growth and fetal programming. *Proceedings of the Nutrition Society* **57**, 105–111.
- Godfrey K, Robinson S, Barker DJP, Osmond C & Cox V (1996) Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *British Medical Journal* **312**, 410–414.
- Gluckman PD (1995) The endocrine regulation of fetal growth in late gestation: the role of insulin-like growth factors. *Journal of Clinical Endocrinology and Metabolism* **80**, 1047–1050.
- Gluckman PD & Harding JE (1997) The physiology and pathophysiology of intrauterine growth retardation. *Hormone Research* **48**, Suppl. 1, 11–16.
- Haig D & Graham C (1991) Genomic imprinting and the strange case of the insulin-like growth factor II receptor. *Cell* **64**, 1045–1046.
- Han VKM & Carter AM (2000) Spatial and temporal patterns of expression of messenger RNA for insulin-like growth factors and their binding proteins in the placenta of man and laboratory animals. *Placenta* **21**, 289–305.
- Harding JE & Johnston BM (1995) Nutrition and fetal growth. *Reproduction, Fertility and Development* **7**, 539–547.
- Hata T, Hashimoto M, Manabe A, Aoki S, Iida K, Masumura S & Miyazaki K (1998) Maternal and fetal nitric oxide synthesis is decreased in pregnancies with small for gestational age infants. *Human Reproduction* **13**, 1070–1073.
- Hawkins P, Steyn C, Ozaki T, Saito T, Noakes DE & Hanson MA (2000) Effect of maternal undernutrition in early gestation on ovine fetal blood pressure and cardiovascular reflexes. *American Journal of Physiology* **279**, R340–R348.
- Heasman L, Clarke L, Stephenson TJ & Symonds ME (1999) The influence of maternal nutrient restriction in early to mid-pregnancy on placental and fetal development in sheep. *Proceedings of the Nutrition Society* **58**, 283–288.
- Heyner S, Smith RM & Schultz GA (1989) Temporally regulated expression of insulin and insulin-like growth factors and their receptors in early mammalian development. *Bioessays* **11**, 171–176.
- Hook EB (1980) Influence of pregnancy on dietary selection. *International Journal of Obesity* **4**, 338–340.
- Huxley RR (2000) Nausea and vomiting in early pregnancy: its role in placental development. *Obstetrics and Gynecology* **95**, 779–782.
- Iatrakis GM, Sakellaropoulos GG, Kourkoubas AH & Kabounia SE (1988) Vomiting and nausea in the first 12 weeks of pregnancy. *Psychotherapy and Psychosomatics* **49**, 22–24.
- Illsley NP (2000) Glucose transporters in the human placenta. *Placenta* **21**, 14–22.
- Jarnfelt-Samsioe A, Samsioe G & Velinder GM (1983) Nausea and vomiting in pregnancy: a contribution to its epidemiology. *Gynecologic and Obstetric Investigation* **16**, 221–229.
- Jednak MA, Shadigian EM, Kim MS, Woods ML, Hooper FG, Owyang C & Hasler WL (1999) Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. *American Journal of Physiology* **277**, G855–G861.
- Ketelslegers JM, Maiter D, Maes M, Underwood LE & Thissen JP (1996) Nutritional regulation of the growth hormone and insulin-like growth factor-binding proteins. *Hormone Research* **45**, 252–257.
- Klebanoff MA, Koslowe PA, Kaslow R & Rhoads GG (1985) Epidemiology of vomiting in pregnancy. *Obstetrics and Gynecology* **66**, 612–616.
- Lopez MF, Dikkes P, Zurakowski D & Villa-Komaroff L (1996) Insulin-like growth factor II affects the appearance and glycogen content of glycogen cells in the murine placenta. *Endocrinology* **137**, 2100–2108.
- Lumey LH (1998a) Reproductive outcomes in women prenatally exposed to undernutrition: a review of findings from the Dutch famine birth cohort. *Proceedings of the Nutrition Society* **57**, 129–135.



- Lumey LH (1998b) Compensatory placental growth after restricted maternal nutrition in early pregnancy. *Placenta* **19**, 105–111.
- McCraib GJ, Egan AR & Hosking BJ (1992) Maternal under-nutrition during mid-pregnancy in sheep: variable effects on placental growth. *Journal of Agricultural Science, Cambridge* **118**, 127–132.
- Maes BD, Spitz B, Ghoois YF, Hiele MI, Evenpoel P & Rutgeerts PJ (1999) Gastric emptying in hyperemesis gravidarum and non-dyspeptic pregnancy. *Alimentary Pharmacology and Therapeutics* **13**, 237–243.
- Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T & Nakao K (1997) Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nature Medicine* **3**, 1029–1033.
- Minniti CP, Kohn EC, Grubb JH, Sly WS, Oh Y, Muller HL, Rosenfeld RG & Helman LJ (1992) The insulin-like growth factor II (IGF-II)/mannose 6-phosphate receptor mediates IGF-II-induced motility in human rhabdomyosarcoma cells. *Journal of Biological Chemistry* **267**, 9000–9004.
- Mori M, Amino N, Tamaki K & Tanizawa O (1988) Morning sickness and thyroid function in normal pregnancy. *Obstetrics and Gynecology* **72**, 355–359.
- O'Dell SD & Day IN (1998) Insulin-like growth factor II (IGF-II). *International Journal of Biochemistry and Cell Biology* **30**, 767–771.
- Ong K, Kratzsch J, Kiess W, Costello M, Scott C & Dunger D (2000) Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-II/mannose-6-phosphate receptor in term human infants. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Journal of Clinical Endocrinology and Metabolism* **85**, 4266–4269.
- Profet M (1988) The evolution of pregnancy sickness as a protection to the embryo against Pleistocene teratogens. *Evolutionary Theory* **8**, 177–190.
- Ravelli ACJ, van der Meulen JHP, Osmond C, Barker DJ & Bleker OP (1999) Obesity at the age of 50 y in men and women exposed to famine prenatally. *American Journal of Clinical Nutrition* **70**, 811–816.
- Reynolds TS, Stevenson KR & Wathes DC (1997) Pregnancy-specific alterations in the expression of the insulin-like growth factor system during early placental development in the ewe. *Endocrinology* **138**, 886–897.
- Robinson J, Chidzanja S, Kind K, Lok F, Owens P & Owens J (1995) Placental control of fetal growth. *Reproduction, Fertility and Development* **7**, 333–344.
- Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Schroeder-Tanka JM, van Montfrans GA, Michels RP & Bleker OP (2000a) Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. *Heart* **84**, 595–598.
- Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ & Bleker OP (2000b) Plasma fibrinogen and factor VII concentrations in adults after prenatal exposure to famine. *British Journal of Haematology* **111**, 112–117.
- Scholl TO, Hediger ML, Schall JI, Mead JP & Fischer RL (1995) Maternal growth during adolescent pregnancy. *Journal of the American Medical Association* **274**, 26–27.
- Schubring C, Kiess W, Englaro P, Rascher W, Dotsch J, Hanitsch S, Attanasio A & Blum WF (1997) Levels of leptin in maternal serum, amniotic fluid, and arterial and venous cord blood: relation to neonatal and placental weight. *Journal of Clinical Endocrinology and Metabolism* **82**, 1480–1483.
- Semmens JP (1971) Female sexuality and life situations. An etiologic psycho-socio-sexual profile of weight gain and nausea and vomiting in pregnancy. *Obstetrics and Gynecology* **38**, 555–563.
- Signorello LB, Harlow BL, Wang S & Erick MA (1998) Saturated fat intake and the risk of severe hyperemesis gravidarum. *Epidemiology* **9**, 636–640.
- Sipiora ML, Murtaugh MA, Gregoire MB & Duffy VB (2000) Bitter taste perception and severe vomiting in pregnancy. *Physiology and Behavior* **69**, 259–267.
- Soules MR, Hughes CL, Garcia JA, Livengood CH, Prystowsky MR & Alexander E (1980) Nausea and vomiting of pregnancy: role of human chorionic gonadotropin and 17-hydroxyprogesterone. *Obstetrics and Gynecology* **55**, 696–700.
- Stein ZA, Susser M, Saenger G & Marolla F (1975) *Famine and Human Development: The Dutch Hunger Winter of 1944–1945*. New York: Oxford University Press.
- Straus DS & Takemoto CD (1990) Effect of dietary protein deprivation on insulin-like growth factor (IGF)-I and -II, IGF binding protein-2, and serum albumin gene expression in rat. *Endocrinology* **127**, 1849–1860.
- Straus DS, Ooi GT, Orłowski CC & Rechler MM (1991) Expression of the genes for insulin-like growth factor I (IGF-1), IGF-2 and IGF binding protein 1 and 2 in fetal rat under conditions of intrauterine growth retardation caused by maternal fasting. *Endocrinology* **128**, 518–525.
- Symonds ME, Budge H, Stephenson T & McMillen IC (2001) Fetal endocrinology and development – manipulation and adaptation to long-term nutritional and environmental challenges. *Reproduction* **121**, 853–862.
- Tierson FD, Olsen CL & Hook EB (1986) Nausea and vomiting of pregnancy and association with pregnancy outcome. *American Journal of Obstetrics and Gynecology* **155**, 1017–1022.
- Tsang IS, Katz VL & Wells SD (1996) Maternal and fetal outcomes in hyperemesis gravidarum. *International Journal of Gynaecology and Obstetrics* **55**, 231–235.
- van Kleffens M, Groffen C, Lindenbergh-Kortleve DJ, van Neck JW, Gonzalez-Parra S, Dits N, Zwarthoff EC & Drop SL (1998) The IGF system during fetal-placental development of the mouse. *Molecular and Cellular Endocrinology* **140**, 129–135.
- Wallace JM (2000) Nutrient partitioning during pregnancy: adverse gestational outcome in overnourished adolescent dams. *Proceedings of the Nutrition Society* **59**, 107–117.
- Wallace JM, Bourke DA, Aitken RP & Cruickshank MA (1999) Switching maternal dietary intake at the end of the first trimester has profound effects on placental development and fetal growth in adolescent ewes carrying singleton fetuses. *Biology of Reproduction* **61**, 101–110.
- Wallace JM, Da Silva P, Aitken RP & Cruickshank MA (1997) Maternal endocrine status in relation to pregnancy outcome in rapidly growing adolescent sheep. *Journal of Endocrinology* **155**, 359–368.
- Weigel MM & Weigel RM (1988) The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. *American Journal of Epidemiology* **127**, 562–570.
- Weigel MM & Weigel RM (1989) Nausea and vomiting of early pregnancy and pregnancy outcome: an epidemiological study. *British Journal of Obstetrics and Gynaecology* **96**, 1304–1311.
- Westwood M (1999) Role of insulin-like growth factor binding protein 1 in human pregnancy. *Reviews of Reproduction* **4**, 160–167.
- Zaina S & Squire S (1998) The soluble type 2 insulin-like growth factor (IGFII) receptor reduces organ size by IGF-II mediated and IGF-II independent mechanisms. *Journal of Biological Chemistry* **273**, 28610–28616.
- Zhou J & Bondy C (1992) Insulin-like growth factor-II and its binding proteins in placental development. *Endocrinology* **131**, 1230–1240.