REVIEW ARTICLES

# Nutritional causes of impaired fetal growth and their treatment

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For the multiple causes of impaired fetal growth a simple classification has been proposed, dividing them into chromosomal, toxic, infective and nutritional[1]. In the first three of these, fetal growth is impaired because of the effects on cell division in embryonic or early fetal development. These causes will not be discussed further in this article. The most common and potentially most treatable cause of impaired fetal growth is nutritional.

## NUTRITIONAL REGULATION OF FETAL GROWTH

Work in animals leaves little doubt that nutrition is an important regulator of fetal growth in late gestation. In fetal sheep, where increments can be measured day to day, growth slows within about three days after the onset of maternal undernutrition and resumes promptly with maternal refeeding[2]. Somewhat similar findings are recorded in case reports of human pregnancies. Severe maternal undernutrition, usually with some medical cause, has been reported to be associated with poor fetal growth, and ultrasound monitoring has shown improvement of fetal growth with measures such as intravenous supplementation in the mother[3]. However, it has been widely held that nutrition has little influence on human fetal growth under more usual circumstances. Why should this be?

First, confusion has been generated by the failure to distinguish between maternal and fetal nutrition. The fetus must grow at the end of a long and sometimes precarious supply line involving maternal nutrient uptake, nutrient delivery to the placenta via uterine blood flow, transport across the placenta, uptake into the fetus via the umbilical circulation, and incorporation of nutrients into fetal tissues, which is under fetal hormonal regulation[4]. Since the function of this supply line is largely determined by maternal size and health, we should not be surprised that maternal size is an important influence on fetal size. Similarly, given the enormous reserve capacity of this supply line, it is not surprising that large changes in maternal nutrition may have negligible impact on fetal nutrition. Conversely, the fetus may suffer substantial loss of substrate supply if, for example, uterine blood flow or placental function are impaired, without a corresponding change in maternal nutrient intake. When considering the nutritional regulation of fetal growth, fetal nutrition must therefore be distinguished from maternal nutrition.

The second cause of confusion in this area has been the presumption that fetal growth is reflected in birthweight. Although birthweight can be easily and accurately measured, it conveys only limited information about the pattern of fetal growth which has resulted in that final outcome[5]. Various groups have recommended the use of other measurements such as ponderal index or mid-arm circumference to partially overcome this difficulty[6]; however the inadequacies of such approaches are readily demonstrated in animal studies. Relatively brief periods of maternal undernutrition in sheep result in profound changes in organ size and body composition of the fetus at delivery, without affecting birthweight[5,7]. Similarly, variation of the proportion of protein in the diet of pregnant rats has complex and non-linear effects on the growth of the placenta, fetus and various fetal organs[8]. Measurements of fetal growth by repeated ultrasound examination will probably overcome some of these difficulties in human pregnancy, and individualized fetal growth curves have been advocated as one approach to distinguishing babies whose small size at birth is appropriate from those whose growth has truly been impaired[9].

Third, the timing and balance of alterations in maternal nutrition may have profound influence on fetal growth. For example, high carbohydrate intake in early pregnancy followed by low protein intake in late pregnancy is associated with lower than average birthweight in apparently well nourished British women[10]. The nature of these interactions and their implications remains to be explored.

Finally, it is increasingly apparent that fetal growth is under fetal endocrine control. In particular, insulin and the insulin-like growth factors (IGFs) are critical mediators of fetal growth in late gestation. Fetal pancreatectomy[11] and IGF-1 gene deletion[12] both result in fetal growth retardation. However, the fact that increases in fetal plasma insulin[11] or IGF-1[13] concentrations do not substantially increase overall fetal size suggests that neither hormone is directly regulating fetal growth. In turn, these hormones are under fetal nutritional control. Fetal insulin secretion is regulated by fetal glucose and aminoacid concentrations[11]. Similarly, fetal IGF-1 concentrations are regulated by fetal

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glucose and insulin concentrations[14]. Thus these data are most easily interpreted as suggesting that the fetal endocrine environment is an important mediator of the nutritional regulation of fetal growth.

## NUTRITIONAL TREATMENTS OF IMPAIRED FETAL GROWTH

If fetal nutrition is the major regulator of fetal growth, then we might reasonably conclude that nutrient supplementation will improve fetal growth. Such supplements could at least in theory be offered at any point along the fetal supply line, but the choice has usually fallen on glucose and aminoacids, the major oxidative substrates for most mammalian fetuses in late gestation.

### Maternal supplements

One reason for the widely held belief that nutrition has little influence on fetal growth in human pregnancy is that maternal nutrient supplements have scant effect on birthweight. Multiple randomized trials of maternal dietary supplements have been undertaken in many thousands of women in many parts of the world. An overview of these trials suggests that, although balanced calorie and protein supplements in severely undernourished women lead to a small increase in birthweight[15], the effect is quite variable and is minimal in women who are not severely malnourished at the time they become pregnant. Thus maternal dietary supplements are unlikely to be helpful in most cases of impaired fetal growth in Western populations. This is not to suggest that such supplements are entirely without benefit, since there is some evidence that late-gestation calorie supplementation in undernourished women can improve growth of the offspring in the first five years of life[16]. This effect may be mediated at least in part by improved maternal lactation capacity although this has not been adequately investigated.

Furthermore, it is becoming apparent that the balance of both macronutrients and micronutrients at different times in gestation may be critical for fetal growth. For example, in women folate status is significantly related to fetal size, perhaps through its involvement in homocyst(e)ine metabolism[17]. Abnormalities of maternal homocyst(e)ine metabolism are in turn associated with various complications of pregnancy, including pre-eclampsia, which commonly result in poor fetal growth. However, clinical trials to determine whether maternal folate supplementation will improve fetal growth, either directly or indirectly, have not yet been reported.

### Amniotic fluid supplements

The fetus normally swallows large quantities of amniotic fluid in late gestation, and fetuses with congenital anomalies that prevent normal swallowing tend to have impaired growth. The late-gestation human fetus swallows up to 700 mL per day and may obtain as much as 10% or its calorie and protein requirements by this route[4]. Since common causes of impaired fetal growth are altered placental function and subnormal uterine blood flow, an alternative approach to improving fetal nutrition is enteral nutrient supplementation. Carbohydrates and proteins injected into amniotic fluid have been shown to be swallowed by the fetus, digested, absorbed and incorporated into body tissues. In fetal sheep, infusion of nutrients into the fetal gut prevented the onset of growth retardation caused by maternal undernutrition[18]. In human pregnancy, infusion of glucose and aminoacids into the amniotic cavity has been claimed to improve growth, but there are no clear measurements of fetal size or untreated controls against which such intervention could be assessed[19].

### Fetal nutrient supplements

There have been case reports of direct infusion of nutrients to the human fetus but again lack of controls and good measurement of growth hampers interpretation of the data[19]. Certainly in animals, growth restriction can be prevented by intravenous infusion of nutrients. Chronic glucose infusion to the normally growing fetus results in larger fetal sheep which have increased body fat[20]. Also in sheep, intravenous infusion of a commercial parenteral nutrition mixture of glucose and aminoacids prevented the growth restriction induced by placental embolization[21]. Direct fetal supplements have the potential advantage that any compromise in the fetal supply line is bypassed. However, the difficulties of suitable access in human pregnancy remain to be overcome.

## DIFFICULTIES WITH NUTRITIONAL TREATMENT OF IMPAIRED FETAL GROWTH

Although fetal nutrient supplements are a potentially valuable approach to the treatment of fetal growth impairment, many issues remain to be overcome. First, it is not clear that, once established, fetal growth impairment is readily reversible. Most of the work in animals indicates that nutrient supplements can prevent the onset of growth impairment, but in no case has the growth impairment been demonstrably reversed once it is established. In sheep, fetal growth slows with the onset of maternal undernutrition and resumes after ten days with maternal refeeding. If maternal undernutrition is prolonged for twenty-one days, fetal growth does not resume upon maternal refeeding; thus growth retardation seems at some point to become irreversible[22]. These irreversible changes may be due at least in part to fetal hormone resistance[23]—an important issue to address before intrauterine therapy can become a

realistic option. This irreversibility of impaired fetal growth may be reflected in the postnatal growth failure seen in many infants born small for gestational age.

In addition, it seems that some aspects of the nutritional regulation of fetal growth may extend over more than one generation. Studies of the Dutch 'hunger winter' at the end of the Second World War have shown that women exposed to famine in early gestation gave birth to babies of normal size, but the girl babies in their turn grew up to have babies who were on average of lower birthweight[24]. There is substantial epidemiological evidence that women who were themselves small at birth have a high risk of giving birth to small babies[25]. In chronically undernourished rats, restoration of normal diet did not result in restoration of normal size and three generations were required before fetal growth and adult size returned to normal[26]. Thus maternal nutrient supplements may not reverse impaired fetal growth immediately, and the effect may not be achieved even in the next generation.

The second difficulty in the nutritional treatment of impaired fetal growth is that such nutrient supplements are not without risk. In this regard, it is useful to think of fetal growth as normally being nutritionally limited. However, the nutrient which is most limiting may vary from time to time and between individuals. Thus, relief of the scarcity of the critical limiting nutrient will increase fetal growth only to the extent that the next nutrient becomes limiting. This concept of the 'next limiting nutrient' is best illustrated in experiments involving nutritional supplementations. Glucose infusion to the normally oxygenated fetus results in an obligatory increase in oxygen demand and a corresponding fall in fetal oxygenation[27]. Such a fall in $PO_2$ and pH in response to fetal glucose administration has been demonstrated in growth restricted human fetuses[28]. Thus additional supply of one nutrient, in this case glucose, may result in increased demand for another, in this case oxygen, which cannot be met. The result may be disadvantageous or even lethal for an already compromised fetus.

Similarly, increased oxygen supply may seem a simple and safe approach to reducing fetal nutrient limitation. Indeed, maternal oxygen supplementation is reported to reduce perinatal mortality in growth-restricted human fetuses[29]. However, the hypoxaemic fetus maintains oxygen supply to essential organs such as the brain and heart by redistributing cardiac output at the expense of peripheral tissues. Maternal oxygen supplementation reverses this adaptation, decreasing the supply to the brain of blood and hence of other nutrients such as glucose and aminoacids[30]. Thus maternal oxygen supplementation may 'improve' fetal blood flow, as assessed by doppler ultrasound, without improving either fetal growth or brain nutrient supply.

Aminoacid supplementation is also not without risk, although the reasons for the adverse effects of aminoacids are not as clearcut. An overview of clinical trials shows that maternal dietary supplementation with a high protein supplement resulted in increased perinatal mortality and reduced fetal growth in many studies[15]. The adverse effects of high concentrations of individual aminoacids are also well known, for example in maternal phenylketonuria. One of the reasons why high aminoacid concentrations have adverse effects may be that individual aminoacids compete for carriers on the placental membranes[31]. In this way excessive quantities of supplemented aminoacids may actually reduce fetal supply of some essential aminoacids. Alternatively, the demand for some essential aminoacids may be increased in order to 'detoxify' the supplemented aminoacids. For example, glycine is required for many synthetic metabolic processes and also for metabolism of methionine. During pregnancy some women have only marginal glycine sufficiency[32]. Supplementary dietary methionine seems to increase demand for glycine and thus limit its availability for other metabolic processes[33]. Given the risk of these various nutrient supplements and the fact that relief of any one limitation may simply result in the next nutrient becoming limiting, supplements containing combinations of nutrients are more likely to be effective.

## CONCLUSION

Fetal growth in late gestation is largely limited by fetal substrate supply. Thus impaired fetal growth is most readily considered a reflection of impaired fetal nutrition. Although supplementary supply of nutrients to the poorly growing fetus is an attractive proposition, it is not yet close to clinical reality. Animal studies to date have shown that supplements can prevent but not reverse impairment of fetal growth. Furthermore, we now know that they carry substantial risks. Provision of combinations of nutrients, perhaps via amniotic fluid to be taken up by the fetal enteral route, seems most promising and remains to be explored in suitable animal models.

There is now a rapidly growing body of published work relating impairment of fetal growth to increased risk of diseases of adult life including ischaemic heart disease and non insulin-dependent diabetes[34]. These observations raise the possibility that nutrient supplements to the poorly growing fetus will eventually provide means to prevent several major disease groups. Much research is now needed to assess the likely benefits and risks of such approaches.

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## REFERENCES


1 Gluckman PD, Harding JE. Fetal growth retardation: underlying endocrine mechanisms and postnatal consequences. *Acta Paediatr* 1997;**422** suppl:69–72

2 Harding JE. Prior growth rate determines the fetal growth response to acute maternal undernutrition in fetal sheep of late gestation. *Prenat Neonat Med* 1997;**2**:300–9

3 Rivera-Alsina ME, Saldana LR, Stringer CA. Fetal growth sustained by parenteral nutrition in pregnancy. *Obstet Gynecol* 1984;**64**:138–41

4 Bloomfield FH, Harding JE. Experimental aspects of nutrition and fetal growth. *Fetal Mat Med Rev* 1998;**10**:91–107

5 Harding JE, Johnston BM. Nutrition and fetal growth. *Reprod Fertil Dev* 1995;**7**:539–47

6 Georgieff MK, Sasanow SR. Nutritional assessment of the neonate. *Clin Perinatol* 1986;**13**:73–89

7 Harding JE. Periconceptual nutrition determines the fetal growth response to acute maternal undernutrition in fetal sheep of late gestation. *Prenat Neonat Med* 1997;**2**:310–19

8 Levy L, Jackson AA. Modest restriction of dietary protein during pregnancy in the rat: fetal and placental growth. *J Dev Physiol* 1993;**19**:113–18

9 Mongelli M, Gardosi J. Reduction of false-positive diagnosis of fetal growth restriction by application of customized fetal growth standards. *Obstet Gynecol* 1996;**88**:844–8

10 Godfrey K, Robinson S, Barker DJP, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *BMJ* 1996;**312**:410–14

11 Fowden AL. The role of insulin in prenatal growth. *J Dev Physiol* 1989;**12**:173–82

12 Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A. Mice carrying null mutations of the genes encoding insulin-like growth factor 1 (IGF-1) and type 1 IGF receptor (IGF1r). *Cell* 1993;**75**:59–72

13 Lok F, Owens JA, Mundy L, Robinson JS, Owens PC. Insulin-like growth factor I promotes growth selectively in fetal sheep in late gestation. *Am J Physiol* 1996;**270**:R1148–R1155

14 Oliver MH, Harding JE, Breier BH, Gluckman PD. Fetal insulin-like growth factor (IGF)-I and IGF-II are regulated differently by glucose and insulin in the sheep fetus. *Reprod Fertil Dev* 1996;**8**:167–72

15 Rush D. Effects of changes in protein and calorie intake during pregnancy on the growth of the human fetus. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press, 1989:255–80

16 Kusin JA, Kardjati S, Houtkooper JM, Renqvist UH. Energy supplementation during pregnancy and postnatal growth. *Lancet* 1992;**340**:623–6

17 Malinow MR, Rajkovic A, Duell PB, Hess DL, Upson BM. The relationship between maternal and neonatal umbilical cord plasma homocyst(e)ine suggests a potential role for maternal homocyst(e)ine in fetal metabolism. *Am J Obstet Gynecol* 1998;**178**:228–33

18 Charlton V, Johengen M. Effects of intrauterine nutritional supplementation on fetal growth retardation. *Biol Neonate* 1985;**48**:125–42

19 Harding JE, Charlton VE. Treatment of the growth-related fetus by augmentation of substrate supply. *Semin Perinatal* 1989;**13**:211–23

20 Stevens D, Alexander G, Bell AW. Effect of prolonged glucose infusion into fetal sheep on body growth, fat deposition and gestation length. *J Dev Physiol* 1990;**13**:277–81

21 Charlton V, Johengen M. Fetal intravenous nutritional supplementation ameliorates the development of embolization-induced growth retardation in fetal sheep. *Pediatr Res* 1987;**22**: 55–61

22 Mellor DJ, Murray L. Effects on the rate of increase in fetal girth of refeeding ewes after short periods of severe undernutrition during late pregnancy. *Res Vet Sci* 1982;**32**:377–82

23 Gluckman PD, Cutfield W, Harding JE, *et al*. Metabolic consequences of intrauterine growth retardation. *Acta Paediatr* 1996;**417** suppl:3–6

24 Lumey LH, Stein AD. Offspring birth weights after maternal intrauterine undernutrition: a comparison within sibships. *Am J Epidemiol* 1997;**146**:810–19

25 Klebanoff MA, Meirik O, Berendes HW. Second-generation consequences of small-for-dates birth. *Pediatrics* 1989;**84**:343–7

26 Stewart RJC, Sheppard H, Preece R, Waterlow JC. The effect of rehabilitation at different stages of development of rats marginally malnourished for ten to twelve generations. *Br J Nutr* 1980;**43**:403–12

27 Phillips AF, Porte PJ, Stabinsky S, Rosenkrantz TS, Raye JR. Effects of chronic fetal hyperglycemia upon oxygen consumption in the ovine uterus and conceptus. *J Clin Invest* 1984;**74**:279–86

28 Nicolini U, Hubinont C, Santolaya J, Fisk NM, Rodeck CH. Effects of fetal intravenous glucose challenge in normal and growth retarded fetuses. *Horm Metab Res* 1990;**22**:426–30

29 Battaglia C, Artini PG, D'Ambrogio G, Galli PA, Segre A, Genazzani AR. Maternal hyperoxygenation in the treatment of intrauterine growth retardation. *Am J Obstet Gynecol* 1992;**167**:430–5

30 Harding JE, Owens JA, Robinson JS. Should we try to supplement the growth retarded fetus? A cautionary tale. *Br J Obstet Gynaecol* 1992;**99**:707–10

31 Kudo Y, Boyd CAR. Transport of amino acids by the human placenta: predicted effects thereon of maternal hyperphenylalaninaemia. *J Inher Metab Dis* 1990;**13**:617–26

32 Jackson AA, Persaud C, Werkmeister G, McClelland IS, Badaloo A, Forrester T. Comparison of urinary 5-L-oxoproline (L-pyroglutamate) during normal pregnancy in women in England and Jamaica. *Br J Nutr* 1997;**77**:183–96

33 Meakins TS, Persaud C, Jackson AA. Dietary supplementation with L-methionine impairs the utilization of urea-nitrogen and increases 5-L-oxoprolinuria in normal women consuming a low protein diet. *J Nutr* 1998;**128**:720–7

34 Barker DJP. *Mothers, Babies and Health in Later Life*, 2nd edn. London: Churchill Livingstone, 1998