

Factors Influencing Fetal Growth

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Abstract

Birth weight remains one of the most important measures we have of the health status of a population, and is a strong predictor of both neonatal mortality and morbidity. It reflects maternal nutritional status and fetal growth rates in the antenatal period. Although a large number of physiological and pathological variables can affect the growth rate, for most cases of growth-restricted fetuses a cause cannot be determined. Awareness of the physiological aspects of fetal growth is important in assessing whether the fetus is growing normally. This article is a review of recent findings and key historical material on factors influencing birth weight.

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Introduction

Birth weight remains one of the most important measures we have of the health status of a population, being a strong predictor of both mortality and morbidity, and reflecting nutritional status and growth rates. Yet, the estimation of the normal growth potential — and hence the definition of growth retardation — for a given individual has remained an elusive objective.

Neonatal size can be influenced by a large number of variables. Kramer,¹ in a lengthy review on low birth weight, listed 43 potential causes, subdivided into 7 groups, while admitting that his literature search may not have been complete. For the purposes of our discussion, we will attempt to classify them as either pathological or physiological, depending on whether or not they are associated with adverse perinatal outcome. This classification will be arbitrary for many of these factors, because of our limited knowledge in this field.

Biochemical and Genetic Control of Fetal Growth

Fetal growth is subject to genetic variation, but the intrauterine environment also exerts a dominant influence. In a study examining the outcome of ovum donation, Brooks et al² found that there was no correlation between donor size and birth weight, whereas the latter was significantly correlated with recipient mothers' weight. Likewise, paternal height has a small correlation with birth weight, with an effect of 40 g per standard deviate of height,³ or about 1% of birth weight. Further support comes from a recent study by Johnston et al⁴ who examined sequence variation in the coding region of the insulin-like

growth factor-I (IGF-I) gene in small for gestational age (SGA) and appropriate for gestational age (AGA) individuals. Although a novel polymorphism in intron-2 was detected, they found that genetic variation of IGF-I alone does not result in SGA birth weights.

Experimental studies of knockout mice have defined the main roles of IGF-I, IGF-II, insulin and their receptors in embryonic and fetal growth. They have provided compelling evidence that increased IGF-II gene expression or abundance can stimulate excessive fetal somatic growth. The IGF-II gene is usually expressed only by the paternally derived allele; however, when this imprinting is erased and IGF-II expression is biallelic, fetal overgrowth ensues.⁵

Leptin is a hormone involved with energy metabolism, which has recently been linked to fetal growth. Varvarigou et al⁶ showed that cord blood leptin levels were lowest in SGA and highest in large for gestational age (LGA) newborns. Geary et al⁷ found maternal leptin levels to be associated with maternal adiposity, and cord leptin levels to be associated with birth weight and subscapular skinfold thickness. It is not clear whether the associations are simply secondary to the amount of adipose tissue, or if abnormalities in secretion are causing growth restriction.

Abnormal nitric oxide metabolism has been mooted as a possible cause of fetal growth restriction. Stearns et al⁸ hypothesised that fetal vascular perfusion may be reduced in fetal growth retardation (FGR) fetuses. Systemic acidosis reduces nitric oxide synthase activity which, in turn, leads to lower nitric oxide levels. In a study of 40 pregnancies, Hata et al⁹ noted that both maternal and fetal nitric oxide

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levels were lower in pregnancies resulting in SGA infants.

Physiological Factors

Parental Size

The relationships between birth weight and parental size have been studied extensively, both in humans and in animals. The classic studies by Walton and Hammond¹⁰ on crosses between the Shire horse and the Shetland pony showed that the birth weights of foal born to Shetland dams of Shire sires were close to those of pure Shetlands; conversely, foals of shire dams by Shetland sires were close to those of the pure breed. Evidence in humans on the preponderance of the maternal effects on fetal growth has been presented by Cawley et al¹¹ and Ounsted.¹² Both maternal height and weight have positive correlations with birth weight, the latter being the stronger factor.

Low maternal pre-pregnancy weight is significantly correlated with both preterm delivery and low birth weight.¹³ On the other hand, obesity, as measured by the body mass index, is only weakly correlated with birth weight.¹⁴ However, the parents' own birthweight is significantly correlated with their offspring's.¹⁵

Parity

The positive effect of parity on birth weight has been documented in most races and in many mammalian species,^{12,16} suggesting that its mechanism may have an evolutionary advantage. Garn¹³ has argued, on epidemiological grounds, that the effect of parity is a result of the increase in the maternal pre-pregnancy weight seen in developed countries, rather than an independent factor. This does not agree with multiple regression analysis of birth weight, which shows parity to be a factor independent of mid-pregnancy weight;¹⁴ this may be because the mid-pregnancy weight is a compound variable, dependent on both the pre-pregnancy weight and maternal weight gain.

There is some evidence that the effect is partner-specific, i.e., a change in partner may be associated with a reduction in the birth weight of the firstborn of the new relationship.¹⁷

It may be argued that because of the significant increase in the perinatal mortality of firstborn infants and those of mothers of high parity, this factor should be classified as a pathological variable. The odds ratios, however, are only slightly elevated¹⁸ and do not justify this re-classification.

Race

Meredith¹⁹ published an extensive description of the variations in birth weight among different ethnic groups. Of the 78 groups considered, the largest newborns were found in Anguilla and Nevis, weighing a mean of 3.88 kg. The smallest babies were those of the Lumi tribe in the Toricelli mountains in New Guinea, with a mean birth weight of 2.4 kg. These ethnic differences clearly persist in

mixed populations from the same location.^{14,20} Birth weight variations do not always correlate with trends in perinatal mortality. In Singapore, Malay babies had a higher perinatal mortality than Indian babies, even though their percentage of low birth weight (<2500 g) was significantly smaller,²¹ with both groups living in similar socio-economic conditions with good healthcare coverage. Similarly, Californian black babies under 3001 g had much lower mortality rates than whites, even though their birth weights were lower.²²

Sex

The female newborn weighs, on the average, 118 g less than the male.¹⁴ This has been observed in most ethnic groups studied.¹⁹ Animal studies suggest that the XY embryo has a growth advantage at the earliest stages of organogenesis;²³ hormonal differences are not responsible, since the sex differences are noted even in anencephalic fetuses. It is of interest that, in spite of this, females born preterm have lower mortality and morbidity than males.²⁴ This may be due to female infants having relatively more energy stores in adipose tissue than males.²⁵

Others

Women with a history of SGA infants are more likely to give birth to small babies. It is not clear whether this is due to genetic factors or recurrence of genetic/pathological factors. Work performed by Ounsted and Ounsted²⁶ has shown that mothers who have borne SGA infants had themselves lower than average birth weights, although their adult height did not differ significantly from that of women who had given birth to babies of normal weight.

Consanguinity in parents has been shown to cause a significant reduction in birth weight in Pakistan,²⁷ Japan²⁸ and Norway.²⁹

Maternal age may affect fetal growth. Clausson et al³⁰ analysed a computerised database of nearly 100,000 ultrasound-dated cases from the Swedish birth register. They found that older (>30 years) nulliparous women and those with hypertensive diseases were at increased risk of both term and preterm SGA infants. Risk factors for being SGA, and mortality rates for SGA infants, varied with gestational age and were highest in the preterm period.

Excessive maternal exertion and heavy physical work in pregnancy have traditionally been linked to poor obstetric outcome. However, Alderman et al,³¹ in a retrospective study, found that moderate maternal physical activity in the second and third trimesters was associated with a significant decrease in the risk of having an LGA infant [odds ratio (OR), 0.3; 95% confidence interval (CI), 0.2-0.7], and no increase in risk of having an SGA infant and no effect on length of gestation.

A seasonal trend has been observed in birth weights, with significantly lower values in summer and a peak in winter/

early spring.³² These fluctuations are rather minor, occurring within a 100-g band.

Pathological Factors

A large number of pregnancy complications are associated with reduced birth weight. Classically, growth retardation has been classified as either symmetric or asymmetric,³³ depending on whether the fetal body dimensions are proportionately reduced, or whether some degree of “head sparing” has occurred. In practice, asymmetric intrauterine growth restriction (IUGR) is associated with either pre-eclamptic toxemia or recurrent abruption, while most other causes lead to symmetric IUGR.

Hypertensive Disease

Essential, uncomplicated hypertension poses little or no risk to the fetus. In early onset or severe pre-eclampsia, birth weight may be reduced by 300 to 500 g and birth length by 1 to 3 cm, whereas late onset or mild pre-eclampsia has no such association.^{34,35} Reduced utero-placental blood flow is considered to be responsible for reduced growth.

Thrombophilias

There has been mounting evidence that acquired or congenital coagulation disturbances may have deleterious effects on pregnancy outcome.³⁶ Using multivariate analysis, Schjetlein et al³⁷ showed that a low concentration of plasminogen activator inhibitor type-2 (PAI-2) antigen in plasma is a consistent risk factor for pre-eclampsia and FGR. Verspyck et al³⁸ reported a case of FGR in association with placental infarcts and thrombophilia secondary to a prothrombin gene variant.

Chronic Maternal Illness

Maternal cyanotic heart disease is associated with fetal growth retardation in up to 52% of pregnancies, as opposed to 9% in the acyanotic group.³⁹

Diabetes has complex effects on fetal growth, with a tendency towards larger babies unless associated with vascular disease and advanced maternal age, when growth retardation is more likely. It is the main pathological cause of fetal macrosomia.

Severe chronic respiratory diseases, such as poorly controlled asthma,⁴⁰ cystic fibrosis⁴¹ and bronchiectasis,⁴² may lead to reduced fetal growth.

In the case of anaemia, it is difficult to separate the effects of anaemia per se from the underlying nutritional problems. However, women with sickle cell disease, sickle-thalassaemia and sickle haemoglobin C disease have an increased incidence of growth-retarded infants.⁴³ This is most likely due to placental micro-infarcts resulting from episodes of sickling, leading to placental insufficiency.

Chronic renal disease of moderate severity is associated with IUGR in up to 24% of cases,⁴⁴ although some of this effect may be related to hypertension.

Systemic lupus erythematosus has been implicated in fetal growth retardation,⁴⁵ though this may be a result of the underlying renal disease or drug therapy.

Abnormal Lipid Metabolism

Changes in maternal lipid metabolism may affect the growth of the fetus. Sattar et al⁴⁶ found that maternal serum cholesterol and low-density lipoprotein (LDL)-cholesterol levels were significantly lower in women carrying FGR fetuses than in unaffected fetuses. This could suggest a failure of appropriate LDL synthesis in FGR pregnancies as a possible aetiological factor for FGR. Cetin et al⁴⁷ studied the fetal-maternal ratios of various lipids in the antenatal period. They reported that the ratio was significantly higher for linoleic acid, significantly lower for the long-chain polyunsaturated fatty acid docosahexaenoic acid and arachidonic acid in growth-restricted, compared with normal, pregnancies. The differences observed could be related to inadequate transplacental supply and to a fetal lack of the enzymes necessary for the production of these essential fatty acids. It was postulated that these differences might have a role in determining the biochemical environment leading to the complications associated with IUGR.

Maternal Addictions

Smoking mothers have babies that are 150 to 200 g lighter than those of non-smokers;⁴⁸ this appears to be caused by smoking in itself rather than other factors associated with the smoker.⁴⁹ Excessive alcohol intake may result in small babies with shortened palpebral fissures and a small head — the fetal alcohol syndrome.⁵⁰ Fetal weight is reduced by 165 to 200 g among mothers who drink the equivalent of more than 50 mL of absolute alcohol per day.⁵¹

Heroin addiction has also been associated with reduced fetal growth.⁵²

Exposure to Medications

There is concern that the practice of prescribing repeated doses of antenatal steroids may cause FGR. There is evidence that this is the case in animal models,⁵³ but human studies are limited. An observational study by French et al⁵⁴ suggested that birth weight ratio decreased with increasing number of antenatal corticosteroid courses and the latter were not associated with demonstrable benefit. Follow-up studies of these infants at age 3 could not detect significant differences in development, although longer-term effect could not be excluded.

Some beta-blocking agents, such as propranolol and

atenolol, have been linked to reduced fetal growth.

High Altitude

Babies born at high altitude are lighter than those born at ground level;⁵⁵ this appears to be a “dose-response” effect related to chronic hypoxia, with smaller babies being born at higher altitude.⁵⁶ Interestingly, both of these studies showed higher rates of preterm delivery.

Malnutrition

Maternal malnutrition, when severe, may result in adverse neonatal outcome. Stein and Susser,⁵⁷ in their classic study, analysed the birth statistics in Holland during the famine of 1944 to 1945; they found that birth weights declined by about 10% only when under-nutrition occurred in the third trimester, with a caloric intake below 1500 g. This is to be expected, since the period of greatest absolute growth is in the last 10 weeks of gestation, when the average fetus gains about 2000 g during this interval.⁵⁸

Placental Disorders

Deep placentation in humans necessitates a physiological transformation of the spiral arteries into uteroplacental vessels. This change involves the inner myometrial segment (junctional zone) of the spiral arteries and is brought about by trophoblast invasion of the vessel wall, resulting in complete loss of the arterial structure and deposition of fibrinoid and fibrous tissues. Absent or inadequate physiological adaptation in the junctional zone spiral arteries limits placental blood flow in pregnancies complicated by pre-eclampsia and fetal growth restriction. The cause of defective deep placentation remains unknown, although it is often attributed to impaired trophoblast function and migration. However, trophoblast invasion is preceded by decidual remodelling of maternal tissues, a process that is initiated in the endometrium but extends into the junctional zone.

Detailed stereoscopic examination of placentae in cases of fetal growth restriction has shown reduced volumes of intervillous space and all types of villi (stem, intermediate and terminal). This reduced growth of peripheral villi affected all tissues (trophoblast, stroma and capillaries), with smaller exchange surface areas and a thicker trophoblastic epithelium. However, the mean diameters of villi and capillaries are generally not affected. These changes are likely to reduce transplacental oxygen diffusion and potentially fetal hypoxic stress.⁵⁹

Recent ultrasound studies have shown that an abnormal circulation in the uterine arteries may lead to poor placental perfusion and ultimately fetal growth restriction and pre-eclampsia.⁶⁰⁻⁶² Abnormal flow velocity waveforms of the uterine arteries occur early in pregnancy (18 to 22 weeks) and include notching and elevated resistivity indices. The detection of these changes may be useful for clinical

screening purposes.

Recurrent antepartum haemorrhages in the first and second trimesters are strongly related to reduced fetal growth, possibly due to impaired development of the uteroplacental circulation.³⁵ Other placental anomalies associated with SGA infants include circumvallate placenta and large chorioangiomas. A rare condition known as massive perivillous fibrinoid may be responsible for recurrent pregnancy failure.⁶³

Infection

Viral infections, particularly rubella and cytomegalovirus, may reduce fetal weight and length to 80% to 85% of normal values.^{64,65} In fatal cases of rubella, the growth restriction is associated with markedly reduced cell numbers in the fetal organs.⁶⁶ Infection with *Listeria* is sometimes associated with IUGR.

In global terms, malaria is probably the most important infectious agent associated with growth restriction on a world-wide basis. This is related to haemolytic anaemia and placental insufficiency related to placental infestation. The pathological changes observed in the placenta include perivillous fibrinoid deposits, syncytiotrophoblast necrosis and partial loss of microvilli. A brownish discoloration may be observed (plasmodial placental pigmentation). These cases are associated with significantly lower birth weights.^{67,68}

Chromosomal Defects

Most chromosomal and genetic disorders are associated with impaired fetal growth of varying severity. In Down's syndrome, birth weight is 80% to 90% of normal, while for trisomy 13 and Turner's syndrome, it is 80% and 84%, respectively.⁶⁹ More severe growth restriction is observed in fetuses with trisomy 18, with an average birth weight of only 62% of normal. Some genetic disorders, such as the Seckel and Russell-Silver syndromes, are associated with severe dwarfing apparent at birth.

On the opposite end of the spectrum, we find a group of genetic disorders associated with fetal growth acceleration. These include Beckwith-Wiedemann syndrome, in which trisomy for the IGF-II gene has been implicated, and “stood” conditions associated with a dramatic increase of fibrous tissue.⁷⁰

In Soto's syndrome, characterised by cerebral gigantism, birth weight is not significantly increased but birth length is increased by a mean of 55.2 cm.

Comments

The distinction between “pathological” and “physiological” factors is, to some extent, arbitrary, with a significantly grey zone of uncertainty. In terms of defining normal growth potential, the maternal physiological factors,

such as height, weight and parity, are probably more important than genetic factors. This distinction is, however, important in order to distinguish the small but healthy fetus from one that is growth-restricted.⁷¹ It is likely that fetal development is under the control of inhibitory and stimulatory growth factors, and that some physiological and pathological factors may well act through common pathways. Animal studies have shed some light on the relative importance of fetal genome and maternal effect; these have been reviewed by Snow.²³ There is good evidence to suggest that maternal effects operate late in gestation, whereas early fetal growth is controlled by fetal genetic mechanisms. Winick⁷² studied the cellular basis of fetal growth using animal models. Three phases of growth were identified: cellular hyperplasia, followed by both hyperplasia and hypertrophy, and then predominantly hypertrophy. Depending on the timing and duration of experimental insults, different forms of growth restriction were observed. Disturbances in early pregnancy restricted the total cell number, so that no “catch-up” growth was possible, whereas later in pregnancy cell size was predominantly affected with minimal reduction in cell numbers, and post-natal recovery was possible with adequate nutrition. This points to the heterogeneous nature of growth disturbances and to the need for using appropriate standards.

It is difficult to determine how much of the differences observed among different ethnic groups are due to genetic factors, as opposed to environmental factors such as nutrition and socio-economic conditions. Hence, customising for ethnicity can only be justified when the adjustment factors are derived from sub-populations in the same location and ideally living under similar socio-economic conditions.

The observed differences in neonatal morbidity between different sub-populations do not always agree with the birth weight differences. This lends weight to the argument that, for optimal performance, fetal weight for gestation as an index of morbidity needs to be evaluated in relation to other pregnancy characteristics. This is now possible in clinical practice by using computer software for generating customised antenatal growth charts.⁷³ In a clinical study, we have shown that these charts significantly reduce the false positive rates for FGR.⁷⁴ They are significantly more accurate at predicting adverse perinatal events, such as intrapartum fetal distress and admission to neonatal intensive care, compared with unadjusted growth standards.⁷⁵

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