Should We Promote Catch-Up Growth or Growth Acceleration in Low-Birthweight Infants?

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Abstract

The idea that catch-up growth or growth acceleration has adverse effects on long-term health has generated much debate. This pattern of growth is most commonly seen after birth in infants of low birthweight; a global problem affecting over 20 million newborns a year. Faster postnatal growth may have short-term benefits but increases the long-term risk of aging, obesity and metabolic disease. Consequently, the optimal pattern of postnatal growth is unclear and is likely to differ in different populations. In infants born prematurely, faster postnatal growth improves long-term cognitive function but is associated with later risk factors for cardiovascular disease. So, on balance, the current policy is to promote faster growth by increasing nutrient intake (e.g. using higher-nutrient preterm formulas). Whether the same policy should apply to larger preterm infants is not known. Similarly, in infants from impoverished environments, the short-term benefits of faster postnatal growth may outweigh long-term disadvantages. However, whether similar considerations apply to infants from countries in transition is uncertain. For term infants from developed countries, promoting catch-up growth by nutritional supplementation has few advantages for short- or long-term health. Overall therefore, a ‘one size fits all’ solution for the optimal pattern of postnatal growth is unlikely.

Introduction

Normally, growth, defined at the simplest level as the quantitative increase in body mass or size, is closely regulated and follows a regular and predictable path. Consequently, monitoring the rate of growth is one of the best indices of a child’s
health, and is an essential part of pediatric care. The pattern of growth is not only a marker of the immediate physical and emotional well-being of the child, but has long-term implications for health. Therefore, historically, achieving adequate growth and the prevention of growth faltering has been the highest priority in clinical research and pediatric practice.

Faltering growth has numerous causes, recovery from which is usually followed by a rate of growth much greater than that expected. This recovery phase of growth, or ‘catch-up growth’, has been a focus of intense research and debate, particularly in light of recent evidence that ‘accelerated’ or too fast growth has detrimental effects on long-term risk of noncommunicable disease. Catch-up growth is most commonly seen immediately after birth in infants with low birth-weight (LBW), a problem which affects over 20 million newborns a year globally [1]. However, the factors contributing to this pattern of growth and its consequences for long-term health are poorly understood. The risk-benefit of faster postnatal growth may differ in different populations (e.g. in infants born pre-term versus those born at term, or in infants from developed or developing countries). As a result, whether postnatal catch-up growth should be actively promoted (e.g. by increasing nutrient intake) remains controversial. The present review considers the evidence for the effects of faster postnatal growth on long-term health, focusing on the biology and clinical impact in term infants from developed countries. It will not address the causes and consequences of postnatal malnutrition (e.g. stunting), a major global issue, known to have adverse effects on long-term adult health and human capital [2].

**Terminology and History**

The phenomenon of a child growing at a rate faster than expected was recognized in the 18th and 19th centuries as the growth pattern in response to recovery from illness [3]. However, this pattern of growth was confused with faster growth associated with the adolescent growth spurt leading to the belief that for the adolescent growth spurt to occur the child had to be first ill. The concept of ‘catch-up’ growth was first formally described in 1954 by Bauer who noted faster growth in 19 children recovering from the nephrotic syndrome [as reviewed, 3]. This work was extended by the demonstration of catch-up growth in several clinical conditions by Prader in 1963 [4]. Importantly, catch-up growth was defined as the acceleration in growth in response to recovery from illness or starvation [4]. Faster growth following recovery was also known by some as ‘compensatory growth’. However, as pointed out by Tanner [3], this term originally referred to the overgrowth of an organ when a part of the organ had been removed.
or to the excess growth of the remaining member of a pair of organs (e.g. kidneys) when one of the pair had been removed.

Catch-up growth was recognized to occur as a natural phenomenon in infancy in the 1950s [3]. Children who were small at birth grew more quickly postnatally than those who were larger (and vice versa). It was assumed that this pattern of growth was the same as catch-up growth and that the infants were recovering from undernutrition in utero. However, early postnatal growth is strongly influenced by genes, and infants with genes for large size but born to small mothers show faster postnatal growth (and vice versa). This reassortment of size occurs soon after birth, and had been described many years previously in animal models. In the classic experiments of Walton and Hammond, foals born to small (Shetland) horses crossed with large (Shire) horses showed faster growth after birth (and vice versa) [as reviewed, 3]. The same phenomenon is seen in humans (see ‘mechanisms’ below). Therefore, faster growth after birth is a natural pattern of growth and is not necessarily the same as catch-up growth (i.e. a consequence of recovery from a period of undernutrition in utero).

A growth rate much faster than expected can also be seen after birth as a consequence of changes in the plane of nutrition. This was first demonstrated in the 1960s by McCance who showed that overfeeding rats during a critical window in early postnatal life permanently increased later body size [5]. Similar effects of a higher plane of early postnatal nutrition occur in humans. Infants born preterm and randomly assigned to a higher-nutrient diet (nutrient-enriched infant formula) compared to a lower-nutrient diet (human milk or standard formula) were found to have greater propensity to obesity, dyslipidemia, raised blood pressure, and insulin resistance in adolescence [6]. Faster growth in infancy was also associated with insulin resistance, markers of inflammation, higher blood pressure and endothelial dysfunction (an early stage in the atherosclerotic process) [6]. Based on these data, and previous epidemiological studies linking faster postnatal weight gain with greater risk of later obesity, we proposed the postnatal ‘growth acceleration’ hypothesis [6]. This concept suggests that upward centile crossing (for weight or length) could explain, in part, the adverse long-term effects on health seen in infants born small for gestation (SGA; who show ‘catch-up’ growth immediately after birth) and long-term cardiovascular benefits in babies breastfed (who are relatively undernourished and have slower growth compared to those given formula) [6]. The term ‘growth acceleration’ was specifically chosen because it makes no assumption about the causes of faster postnatal growth, and it encompasses several potential causes such as faster growth arising from recovery from illness or starvation (i.e. ‘catch-up’ growth), genetic factors or accelerated growth as a consequence of a higher plane of postnatal nutrition.
The Impact of Growth Acceleration on Long-Term Health

The fact that ‘catch-up’ occurs in animal species as diverse as mammals, birds, fish as well as humans suggests that this pattern of growth must be an evolutionary conserved adaptive response [7, 8]. These beneficial effects may include faster maturity and hence greater reproductive success, and greater likelihood of survival as a result of a larger size in early life (e.g. protection from predators, infectious disease or starvation) [7, 8]. However, the fact that humans and animals do not grow as fast as they are capable of (e.g. as seen during catch-up growth) suggests that faster growth in early life must also have a biological cost. Therefore, there is a trade-off in order to optimize growth trajectories between short-term benefits and long-term costs, the concept of ‘grow now pay later’ [7]. The short-term advantages of faster growth in infancy either in those born LBW or SGA is well recognized and include, for example, a lower risk of hospitalization in poorer environments [9]. The long-term cost of this faster growth, however, is an increased risk of noncommunicable disease. Importantly, because the effects of faster postnatal growth on risk of diabetes, CVD, and even, more rapid aging, are usually manifest later in life, after reproduction, these ‘diseases’ are not greatly affected by selective pressures.

The concept that growth acceleration has adverse consequences for long-term health is now strongly supported by a wealth of evidence. The association is biologically plausible and experimentally reproducible in several animal models [10–12]. In humans, faster weight gain in infancy (upward centile crossing for weight) is associated with a greater risk of later obesity in more than 30 studies (summarized in 5 systematic reviews [13–17]). The evidence is consistent across studies [15, 16] and includes an individual-level meta-analysis in 47,661 participants from 10 cohorts [16]. The association between postnatal growth acceleration is consistent for cohorts during the last 80 years [13–15], is seen in breastfed and formula-fed populations, and has been shown to influence the main components of the metabolic syndrome [6, 18]. For instance, in infants born SGA, faster weight gain in the first 3 months of life is associated with lower insulin sensitivity and HDL cholesterol concentrations, and higher triglyceride concentrations, obesity and markers of atherosclerosis at age 18–24 years [18]. Long-term effects of postnatal growth acceleration are evident in both infants born preterm or at term, infants born small or appropriate weight for gestation, in adults as well as children, and in developed and developing countries [19]. For example, in a cohort study from Delhi, rapid gain in BMI in the first year was associated with development of the metabolic syndrome in adulthood [as reviewed, 19]. The effects of faster growth in influencing, or programming, long-term health appear to be greatest for central or visceral adiposity [19], a key risk
factor for CVD and type 2 diabetes. These effects on visceral adiposity are particularly marked in infants born SGA [18, 20]. Overall, these studies suggest a large effect size. For example, over 20% of later obesity risk can be explained by the rate of infant weight gain [12], and the relative risk of later obesity associated with more rapid weight gain in infancy ranges from 1.2 to as high as 5.7 [14].

Importantly, while observational studies may be confounded by genetic and environmental factors which could both promote faster infant growth and increase the risk of later obesity, follow-up of randomized studies, initially in established trials in infants born prematurely [6] or SGA [as reviewed 19], and subsequently in new prospective trials, support a causal link between infant growth and later risk of obesity and CVD [19]. Infants born preterm and randomly assigned to a nutrient-enriched diet, which promoted faster weight gain in the first few weeks after birth, had higher fasting concentrations of insulin, cholesterol, and C-reactive protein, as well as leptin resistance in adolescence than controls [6]. Similarly, infants born SGA at term and randomly assigned to nutrient-enriched formula that increased weight gain had higher diastolic BP at age 6–8 years and, in 2 trials, 18–38% greater fat mass at age 5–8 years than controls [19]. Interestingly, differences in childhood fat mass or blood pressure between randomized groups were related to the rate of weight gain in infancy suggesting a ‘dose-response’ association between early growth and later CVD risk [19]. These programming effects have been confirmed in experimental studies of term infants with appropriate birthweight for gestation and in low-income countries (e.g. Chile [19]), thereby supporting the concept that programming of metabolic disease by faster early growth is a fundamental biological finding seen across populations.

Nevertheless, despite extensive evidence for the growth acceleration hypothesis, several areas of controversy remain. For instance, many have argued that programming effects of postnatal growth acceleration are a consequence of catch-up growth following a period of prenatal growth restraint. In support of this, a systematic review of 50 studies found an increased risk of the metabolic syndrome in infants born LBW who showed ‘catch-up’ growth postnatally [22]. Although it is difficult to disentangle the effects of LBW from faster postnatal growth, because the two are closely interrelated, earlier [10] and more recent animal studies [11] suggest that faster postnatal growth is an independent risk factor for later disease [11]. Observations that the effects of LBW on the adult phenotype can be reversed by preventing postnatal catch-up growth, and that growth acceleration increases the risk of metabolic disease in animals without prenatal growth restriction, support the concept that accelerated postnatal growth per se is the key independent risk factor for later metabolic disease [11]. Whether LBW or prenatal nutrition further exacerbates the effects of faster post-
natal growth is not clear, but is unlikely in view of the fact that no study in humans has shown a statistical interaction between birthweight and postnatal growth on later risk of obesity (i.e. size at birth does not modify the effects of postnatal growth acceleration on later health) [15, 16]. This observation has important implications for the nutritional management of infants born SGA and suggests that optimizing postnatal growth may be beneficial irrespective of the antenatal environment.

**Mechanisms**

Research into the mechanisms for the growth acceleration concept has focused in two main areas: (1) understanding the causes of faster postnatal growth and the physiological mechanisms involved, and (2) unravelling the coupling mechanisms that link a stimulus (such as growth/nutrition) acting during a critical window in early life with later outcomes such as obesity and CVD.

In a recent systematic review, postnatal growth acceleration was associated with smoking during pregnancy, being first born, being born LBW (particularly as a result of intrauterine growth retardation in the 3rd trimester), formula feeding rather than breastfeeding, and earlier introduction of complementary feeding [23]. In addition to these factors, the large Nourish study from Australia identified high maternal BMI, low maternal education levels, male infant gender, and feeding on a schedule (rather than in response to the baby’s hunger cues) as factors increasing the rate of postnatal growth. As in animal models, genetic factors affect the postnatal growth rate, as highlighted by data from the Avon Longitudinal Study of Pregnancy and Childhood, which found that infants showing faster postnatal growth had taller fathers. While many of the factors associated with faster postnatal growth are not modifiable, this research clearly suggests that prevention of both antenatal growth faltering and postnatal overnutrition may have benefits for long-term health.

Several generic hypotheses have been proposed to explain the ‘coupling mechanisms’ linking early exposures such as growth with later biological effects such as CVD. The first, the role of epigenetic changes that persist throughout life, is supported by evidence in animal models. Plagemann et al. [24] showed that neonatal overfeeding in rats (which leads to development of the metabolic syndrome later in life) was associated with increased methylation of CpG residues in the insulin receptor promoter gene. Although this epigenetic change did not affect insulin receptor gene expression in the short-term, the authors speculated that increased methylation of this allele could predispose to insulin insensitivity under adverse environmental conditions later in life.
The second hypothesis proposes that early growth acceleration permanently affects hormonal axes that regulate body weight, food intake and metabolism, and hence fat deposition. Hormonal changes in infancy (possibly via changes to the hypothalamic circuitry regulating appetite) could influence the satiety response and increase food intake throughout life, thereby increasing the risk of obesity and CVD. Postnatal growth acceleration may program a higher set point for appetite, a hypothesis proposed by Widdowson and McCance in 1975 [21] and now supported by extensive evidence from animal and human studies [10, 11, 19].

The third generic hypothesis suggests an adverse effect of faster growth on aging and biochemical factors predisposing to cellular aging (e.g. increased oxidative stress and altered mitochondrial function), a hypothesis first proposed by McCay in the 1930s and seen in numerous animal species [8, 10, 11, 25]. In fact, it has been argued that the accumulation of cellular damage is an inevitable feature of catch-up growth as cellular resources are invested in growth rather than repair [8].

**Implications for Infants Born Low Birthweight**

The evidence suggesting adverse long-term effects of postnatal growth acceleration has generated considerable controversy and debate. The optimal growth trajectory for LBW infants is currently unclear and is likely to differ in different populations. Therefore, the answer to the question ‘to catch-up or not to catch-up’ must lie in balancing the interests of the child according to the cause of LBW and the child’s environment. In preterm infants, for example, faster postnatal growth is associated with the same metabolic risk factors for CVD as in term infants [26], but improves cognitive function [27]. So, on balance, the current policy is to promote faster postnatal growth by increasing nutrient intake (e.g. using higher-nutrient preterm formulas). However, even in preterm infants the optimal growth pattern for the larger preterm infant (>34 weeks’ gestation) is unclear since most of the evidence for the benefits of faster growth for later cognitive function is based on infants born <31 weeks’ gestation [27].

Part of the difficulty in answering the question to ‘catch-up or not to catch-up’ for the large number of LBW infants born in developing countries is that gestational age may not be accurately known. Nonetheless, current WHO policy recommends exclusively breastfeeding or using standard formulas rather than nutrient-enriched formulas from hospital discharge to age 6 months [1]. For LBW infants in extremely impoverished environments, clearly the priority is to prevent malnutrition and growth faltering [1, 2]. Even in low-income countries,
however, massive changes in diet and rise in urbanization means that large sections of society are at increased risk of obesity and CVD and so susceptible to programming effects of early growth [19]. Therefore, whether postnatal upward centile crossing should be promoted in developing countries (as is common in many cultures by using bovine milks or early addition of solid foods) is unknown but unlikely to be beneficial in view of the well-established benefits of exclusively breastfeeding for 6 months.

For infants born SGA in developed countries, contrary to previous medical and public opinion, promoting catch-up growth by nutritional supplementation is unlikely to have any advantages for long-term health [28]. In fact, nutrient-enriched formulas designed to promote faster growth are no longer recommended [1, 28, 29] and exclusive breastfeeding may be particularly advantageous for long-term cognitive development in SGA infants [30]. Overall therefore a ‘one size fits all’ solution for the optimal pattern of postnatal growth is unlikely, and further research will be required to guide nutritional and public health practice in many populations.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

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