

# Accepted Manuscript

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PII: S0002-9378(15)00610-9

DOI: [10.1016/j.ajog.2015.06.027](https://doi.org/10.1016/j.ajog.2015.06.027)

Reference: YMOB 10474

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 1 June 2015

Accepted Date: 8 June 2015

Please cite this article as: Hanson M, Kiserud T, Visser GHA, Brocklehurst P, Schneider E, Optimal fetal growth – a misconception?, *American Journal of Obstetrics and Gynecology* (2015), doi: 10.1016/j.ajog.2015.06.027.

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**Optimal fetal growth – a misconception?**

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The authors report no conflict of interest

***This commentary arose in part from discussions at a workshop 'Beyond Birthweight' held at the University of Sussex on 24-25 October 2014, supported by the Wellcome Trust, the DOHaD Society, the Economic History Society and the University of Sussex Centre for Global Health Policy***

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**Abstract**

Alterations in fetal growth trajectory, either in terms of individual organs or the fetal body, constitute part of a suite of adaptive responses that the fetus can make to a developmental challenge such as inadequate nutrition. Nonetheless, despite substantial changes in nutrition in many countries over recent centuries, mean birthweight has changed relatively little. Low birthweight is recognised as a risk factor for later noncommunicable disease, although the developmental origins of such risk are graded across the full range of fetal growth and birthweight. Many parental and environmental factors, some biological, some cultural, can influence fetal growth, and these should not be viewed as abnormal. We argue that the suggestion of establishing a universal standard for optimal fetal growth ignores the breadth of these normal fetal responses. It may influence practice adversely, through incorrect estimation of gestational age and unnecessary elective deliveries. It raises ethical as well as practical issues.

**Does birthweight matter?**

Apart from the sex of the newborn baby, the information which every parent and health practitioner wants to know is how much the baby weighs. Historically, a reason for this was that infant survival and growth were related to birthweight (1). More recently, birthweight has been linked to risk of later disease, especially non-communicable disease (NCD), and used to provide a measure of prenatal development through the recognition that it is affected by the health, lifestyle and other attributes of the mother such as her age, parity, stature etc. This is the DOHaD concept (2) and, although it has been primarily discussed in relation to effects on fetal nutrition, it is now recognised that many other environmental factors (e.g. stress, unhealthy behaviours, environmental chemicals) also play a role.

A range of epidemiological studies have used birthweight as a proxy measure for the quality of fetal development (3). This has the advantage that birthweight is a widely recorded parameter at birth, although it is still not measured in many low resource settings. However birthweight is a problematic measure of prenatal development because different prenatal environmental exposures, patterns of fetal growth and durations of pregnancy can lead to similar birthweights. Moreover, although socioeconomic factors affecting early life have changed substantially in the past 150 years, and there are large variations in these factors around the world today, they are associated with relatively less variation in birthweight than in other parameters (e.g. height, adiposity). Furthermore, while the focus of most epidemiological studies was on the later health consequences of low birthweight, it is now recognised that high birthweight is also associated with risk of NCDs (4). Low and high birthweights can occur simultaneously in the same community, the same family and even sequentially for the same woman, as socioeconomic changes lead to unhealthy behaviours, obesity, excessive gestational weight gain and higher prevalence of Type 2 diabetes and gestational diabetes (5).

At the population level, the association between birthweight and later risk of non-communicable disease (NCD) is U-shaped, revealing the interaction of multiple factors operating prenatally (6). Populations vary in the width and position of this U-shaped relation, as do ethnic groups. In migrants, changes in socioeconomic conditions (e.g. urbanisation, adoption of a Western lifestyle) are sometimes associated with greater risk of later NCDs but the birthweight distribution does not shift fully to the position of the adopted society. For all these reasons, birthweight seems not to be a very informative variable.

**What controls fetal growth?**

Current ideas about human development have moved away from a deterministic view of a genetic programme towards a more holistic concept, in which genetic and environmental factors interact to influence the development of phenotypic attributes, including birthweight, across the normal range of prenatal life (7).

It is widely believed that the fetus takes what it needs from its mother: indeed epidemiological studies have confirmed that birthweight is relatively unaffected even by severe challenges such as famine. However modern evolutionary and developmental biology thinking suggests that the mother and child are in a competition of sorts because the mother must survive to reproduce again. Basic and clinical research has shown that the result of the maternal-fetal dialogue is a compromise between fetal adaptive responses and maternal constraint of growth(8). What is optimal for the

fetus may not be so for the mother: for example recent studies show that the median birthweight in a population is lower than that which is optimal for perinatal survival(9).

### **The importance of fetal growth**

For the reasons above, a change in birthweight does not necessarily lie on the causal pathway to later disease risk. In cohort studies some prenatal risk factors for later NCDs are not associated with changes in birthweight and it is the trajectory of fetal growth in the second half of gestation which is important. Is it therefore more important to focus conceptually on fetal growth rather than size at birth?

However, one cannot answer this question without considering what fetal growth represents. Because fetal growth is part of the plastic response made by the fetus, it cannot be considered in isolation from the conditions *in utero* which provided the stimulus for that response. The fetal 'strategy' in terms of its growth response involves far more than just size. It includes changes in organ development, some of which are complete at term (no. of nephrons, cardiomyocytes). Other aspects are related to postnatal growth and function (adipose distribution). Others still relate to settings of physiological control processes, e.g. metabolism, appetite. The resulting strategy will allow the fetus to 'tune' its development appropriately for the current conditions (8). The nature of the response depends on that of the stimulus; for example whilst the redistribution of blood flow to the brain and heart under conditions of hypoxia provides one adaptive response, leading if sustained to a particular pattern of asymmetrical growth, the challenge of unbalanced maternal nutrition leads to redistribution of blood flow to the fetal liver and greater fat deposition (10).

The vision of 'optimising' such development, perhaps through improving maternal health, to give the next generation the best start in life, is thus a natural and laudable one. However it raises the question of how to assess whether development is indeed 'optimal'.

### **What is optimal fetal growth?**

This question was recently taken up by the INTERGROWTH-21<sup>st</sup> study (11), which proposes the adoption of a universal standard for fetal growth, based on the proposition that optimal conditions for the mother, in terms of her education, nutrition and relative socioeconomic status in disparate cultural settings will lead to similar patterns of fetal growth. Such growth is therefore deemed to be 'optimal'. At first sight the adoption of such a standard might be thought to make obstetric care more uniform and support efforts to improve maternal nutrition and lifestyle in many settings. However adopting it may lead to over-diagnosing both large and small for gestational age fetuses, in terms of what is appropriate for a particular population, with a corresponding detrimental impact on clinical care. Historical and contemporary data show how population characteristics and aspects of the life course (e.g. age at first conception, interbirth interval, family size) vary over time and location in both migrating and stationary societies. Populations therefore need reference ranges reflecting optimal conditions for a healthy life course under their own conditions, rather than standards derived from mixed relatively affluent urban populations with abundant nutrition and sedentary lifestyles.

The fundamental proposition underlying INTERGROWTH-21<sup>st</sup> is that there is an 'optimal' pattern of human fetal growth which is universal: perhaps because it proceeded from a purely maternal nutritional premise, it takes no account of the developmental plasticity which allows each fetus to

regulate its development. It ignores lessons from history and demography, an attitude which has proved disastrous in other contexts.

### **What are the consequences of a universal fetal growth standard?**

Going beyond the scientific misconceptions underlying a universal standard for optimal fetal growth, there are other wider concerns. If the conditions for optimal fetal growth assumed from INTERGROWTH-21<sup>st</sup> were taken to be necessary in every culture, the adequately adapted patterns of fetal growth in many populations around the world which do not conform to such prescribed optimal conditions might be stigmatised. Clues to the importance of such local cultural and other conditions are present even in the report on INTERGROWTH-21<sup>st</sup>, although they are dismissed: for example whilst BMI did not differ between the eight population groups studied in INTERGROWTH-21<sup>st</sup>, maternal height was lower in India and Oman – countries with lower birthweights. The ethnic or cultural differences in the relation between mother's habitus and fetal growth emphasise that one pattern of fetal growth does not fit all, and basing clinical decisions on the assumption that it does may do more harm than good, for example in over-diagnosing both fetal growth restriction and macrosomia, increasing the incidence of caesarean section with potentially adverse long term consequences.

Adopting a universal fetal growth standard may therefore not be scientifically valid or clinically beneficial. It may exacerbate issues of equity and ethical standards important in women's and children's health (12). Clearly more meaningful predictors of healthy development are needed. As height is linked to life expectancy as well as economic productivity, the relation between maternal height, fetal growth and birthweight merits further consideration. Because fetal adaptive responses to the prenatal environment also involve a range of functions that are not necessarily associated with growth or size, more detailed analysis of physiological function may also be necessary. Thus, epigenetic markers may provide better indicators for the prenatal environment and predictors of later NCD risk and should be studied more closely in the future.

The term 'optimal' should also be used with care. Historically the median birthweight has been regarded as 'normal' or even 'super-normal' in some more refined clinical studies. This might be regarded as one definition of 'optimal', although this is clearly not appropriate for perinatal or for long term survival. Other definitions of 'optimal' development might refer to long-term survival or NCD risk. Others still might refer to Darwinian fitness, i.e. survival to reproductive success. Clearly these definitions will not encompass the same group of foetuses and so the term optimal has to be qualified, defeating its universal applicability.

Thus, we are left with a final question: whose interests should inform a recommendation about what is 'optimal' fetal growth – the mother's, the fetus's, the doctor's, or society's interests?

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TEXT BOX:

Apart from the sex of the newborn baby, the information which every health practitioner and parent wants to know is how much the baby weighs. Birthweight is widely used as a proxy for prenatal development, and both low and high birthweights have been linked to a risk of later ill-health. However, a new set of birthweight and fetal growth ranges were recently suggested as global 'optimal' standards and recommended for general use. They are based on studies of healthy women with good nutrition and high educational and socio-economic status, but are they appropriate in all settings and all countries and what might be the consequences of adopting them?



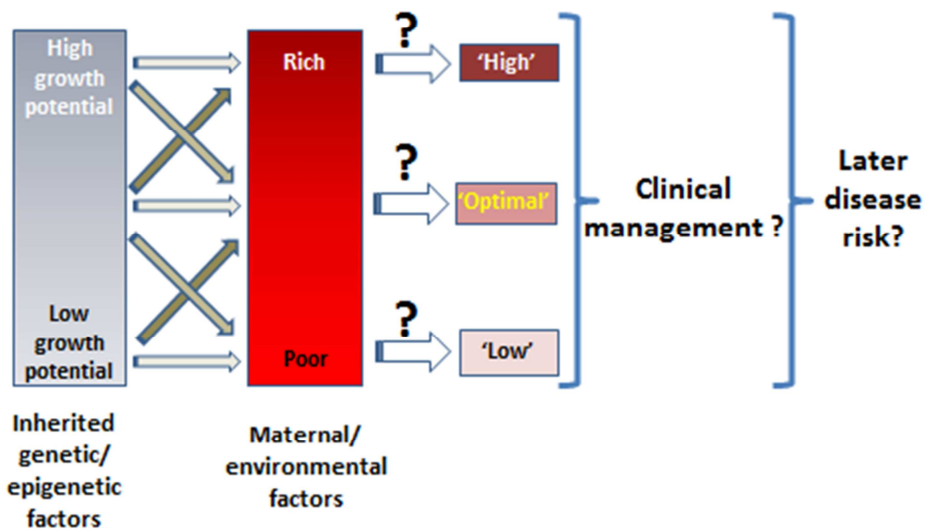


Figure 1. Measured trajectories of fetal growth, from 'low', through 'optimal' to 'high', depend on inherited factors influencing growth potential and also on maternal characteristics and environmental factors. Multiple interactions between these are possible, ranging from matched growth in relation to potential (horizontal arrows), excessive growth such as macrosomia (upward arrows) or growth restriction (downward arrows), which can result in similar measured trajectories. These are therefore not mechanistically meaningful or clinically useful in terms of management or prediction of later disease risk.