Optimal fetal growth: a misconception?

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Apart from the sex of the newborn baby, the information that 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 noncommunicable disease (NCD), and has been 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 Developmental Origins of Health and Disease concept,[2] and, although it has been primarily discussed in relation to effects on fetal nutrition, it is now recognized that many other environmental factors (eg, stress, unhealthy behaviors, 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 (eg, height, adiposity). Furthermore, although the focus of most epidemiological studies was on the later health consequences of low birthweight, it is now recognized 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 behaviors, obesity, excessive gestational weight gain, and a higher prevalence of type 2 diabetes and gestational diabetes.[5]

At the population level, the association between birthweight and later risk of NCD is U shaped, revealing the interaction of multiple factors operating prenatally.[6] Populations vary in the width and position of this U-shaped relationship, as do ethnic groups. In migrants, changes in socioeconomic conditions (eg, urbanization, 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 program toward 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 (Figure).[9]

The importance of fetal growth

For the reasons stated previously, 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 that 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

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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 (number of nephrons, cardiomyocytes). Other aspects are related to postnatal growth and function (adipose distribution). Others still relate to settings of physiological control processes (eg, 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, although 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 optimizing 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 the development is indeed optimal.

What is optimal fetal growth?

This question was recently taken up by the INTERGROWTH-21st 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.

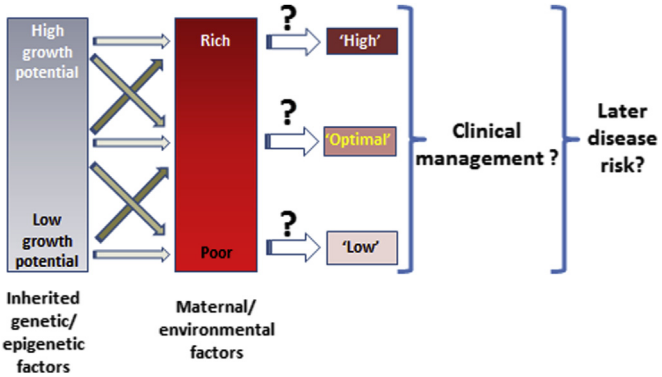
At first sight the adoption of such a standard might be thought to make obstetric care more uniform and support efforts to improve maternal nutrition and lifestyle in many settings. However, adopting it may lead to overdiagnosing both large- and small-for-gestational-age fetuses in terms of what is appropriate 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 (eg, 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-21st is that there is an optimal pattern of human fetal growth that is universal: perhaps because it proceeded from a purely maternal nutritional premise, it takes no account of the developmental plasticity that allows each fetus to regulate its development. It ignores lessons from history and demography, an attitude that has proved disastrous in other contexts.

FIGURE

Measured trajectories of fetal growth, from low through optimal to high



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 relationship 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.

Hanson. Optimal fetal growth. Am J Obstet Gynecol 2015.

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-21st were taken to be necessary in every culture, the adequately adapted patterns of fetal growth in many populations around the world that do not conform to such prescribed optimal conditions might be stigmatized.

Clues to the importance of such local cultural and other conditions are present, even in the report on INTERGROWTH-21st, although they are dismissed: for example, whereas BMI did not differ between the 8 population groups studied in INTERGROWTH-21st, maternal height was lower in India and Oman, countries with lower birthweights.

The ethnic or cultural differences in the relationship between mother's habitus and fetal growth emphasize 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 overdiagnosing both fetal growth restriction and macrosomia, increasing the incidence of cesarean delivery 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. Because height