Commentary: Maternal constraint is a pre-eminent regulator of fetal growth

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A fundamental aspect of human reproduction is the close tolerance between the size of the fetal head at term and of the pelvic canal through which it must pass. Human evolution has favoured the development of a large brain, but this created a conundrum: avoiding obstructed labour means being born so immature that postnatal survival might be reduced; on the other hand delaying birth until brain growth was sufficient for such survival means running the risk of obstructed labour, presumably fatal for both mother and fetus in the absence of modern obstetric care. Such considerations suggest that maternal skeletal dimensions and fetal size at birth must be closely matched, the concept of maternal constraint.¹ But is such matching possible, since skeletal growth has a genetic component which is both paternal and maternal? In 1938 Walton and Hammond addressed this question, showing that at birth foals resulting from crosses between horse breeds of very different body size were more similar in size to the mare than the stallion. Ounsted et al. addressed whether such processes operate in human pregnancy.²

The paper is a landmark in human developmental biology and the issues raised are still researched,

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now using more complex methods such as embryo transfer.\textsuperscript{3} Ounsted et al.’s findings remain valid and provide a classic demonstration of how important conclusions can be drawn from simple observations provided these are made with care and are used to test a clear \textit{a priori} hypothesis. Women of shorter stature have smaller pelvic dimensions, but are nonetheless able to give birth to healthy infants. To examine the matching of fetal growth to the reproductive capacity of the mother, Ounsted et al. used data on newborn singleton infants stratified into those small, appropriate and large-for-dates. This was linked to family history of size at birth. They proposed that maternal constraint slows fetal growth even in \textit{normal} pregnancies, a remarkably prescient idea in the light of current interest in how fetal growth is controlled, and the long-term consequences of normal variations in growth. Thus the maternal effects involve normal biological processes rather than the disruptive effects of an adverse environment, which might be viewed as more akin to the teratological.

We can trace to this paper ideas of how parentally imprinted genes may be involved in maternal–paternal conflict. In the light of this more recent work we might revise Ounsted’s concept to include processes which can accelerate fetal growth. An important conclusion from Ounsted et al. is that only when maternal constraint processes are ‘relaxed’ do Mendelian processes determine fetal growth operate pre-natally. There is much current interest in non-Mendelian methods for examining the influence of the developmental environment. Moreover, the operation of such maternal effects makes it clear that humans share many similarities with other species in which such mechanisms have been shown, and their importance debated, in developmental biology.\textsuperscript{4} Ounsted et al. conclude that maternal constraint may provide a mechanism by which environment is detected by the mother, and induces adaptive changes in the growth of her offspring. This would have adaptive advantage during times of environmental change occurring at a rate too fast for genomic processes to operate. Maternal constraint processes would therefore have been selected during evolution, and cannot be rapidly disengaged. The idea is taken up in recent considerations of how this constraint may enable the fetus to ‘predict’ aspects of its future environment,\textsuperscript{5} highly relevant in today’s world in which socioeconomic progress often produces nutritional and lifestyle changes within a generation, especially in developing societies. The epidemic of obesity, type-2 diabetes and cardiovascular disease are in part the consequence.

Much research today into developmental effects on phenotype of the offspring is concerned with epigenetic processes, a term effectively coined by Conrad Waddington\textsuperscript{6} many years before Ounsted et al.’s paper. The underlying mechanisms include changes in patterns of DNA methylation, in histone protein structure and miRNAs.\textsuperscript{7} Such processes operate in X chromosome inactivation and imprinted genes such as the H19-IGF2 region, which may be involved in maternal constraint of fetal growth. Epigenetic processes also operate much more extensively over the genome and can be affected by maternal diet, glucocorticoids and endocrine disruptors. Maternal constraint appears to be part of a wider phenomenon, by which mothers educate their offspring about certain aspects of the world, even before they are born.

What are the contemporary clinical implications of Ounsted et al.’s work? We believe that two under-recognized implications need particular emphasis, both concerning the clinical measurement of fetal growth. First, studies in pregnant sheep indicate that, in late gestation, maternal influences bear preferentially on fast growing fetuses, presumably because their nutrient requirements are greater.\textsuperscript{8} Recent studies demonstrate that human fetuses also vary substantially in their rates of growth from early gestation onwards,\textsuperscript{9} and that environmental influences can alter the trajectory of fetal growth in the first trimester.\textsuperscript{10} These effects question the now routine clinical practice of preferring ultrasound over menstrual data to establish gestational age in early pregnancy. This will lead to errors in detecting fetuses which are not growing appropriately. The second problem is related, and also needs serious consideration. The World Health Organization has recently concluded its project to define an optimal growth standard for children, and is formulating plans to produce a similar standard for the human fetus. We can see that measurement of fetal growth in the absence of data on maternal constraint processes will be fraught with difficulties in interpretation. Pregnancy involves a collaboration, or perhaps a dialogue is a better analogy, between the mother and her fetus, modulating fetal growth from its genetically determined path in relation to her state, environment and history. This was vital to human evolution, and it is still important today in relation to pregnancy outcome and later health of the offspring. All humans are born equal, but this does not mean that they grew equally as fetuses. It is not that simple—as so elegantly shown by Ounsted et al.

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References

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Commentary: A need for unconstrained thinking on foetal growth

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Foetal growth is a fascinating and poorly understood biological phenomenon in humans. There are two main avenues of interest. One is the study of deviant growth patterns, which is best detected by serial measurements of individual pregnant women in a clinical setting. The other is the analysis and interpretation of data sets, where birth weight or other measures of foetal growth are either the outcome or the exposure. During the last 15–20 years, observations of associations between birth weight and adult disease have created a whole new area of research in response to theories of intrauterine programming. Margaret Ounsted interpreted her studies of the familial co-variation in birth weight in an analogous manner, claiming that the intrauterine environment experienced by a female foetus determines the size of her later newborn children. There is a maternal constraining mechanism on foetal growth, and the set point of the constraining mechanism is adjusted in utero in female foetuses. In crossbreeding, this mechanism will ensure that foetal growth rate matches that of the maternal strain.

The data set that led to the proposition that this maternal constraint exists in humans was based on the families of three types of probands; children who were either small-for-dates (SFD), average-for-dates (AFD) or large-for-dates (LFD). Birth weights of maternal and paternal relatives were compared between these three groups, as illustrated in Table 2 and Figure 1. The birth weights of paternal and maternal relatives were reported by the mothers with the aid of aunts and grandmothers. It was found that the mean birth weights of first-degree relatives (sibs, mother and fathers) followed a regular pattern. The siblings of SFD, AFD and LFD children had mean birth weights of 2734 g, 3274 g and 3963 g, respectively. The mothers’ mean birth weights were 2973 g, 3337 g and 3782 g, respectively, while the fathers’ were 3186 g, 3336 g and 3636 g. One should note the large standard deviations and the relatively small sample sizes.

There is a simple alternative explanation to the observations, namely that of polygenic inheritance taking both the maternal and the foetal genome into consideration. There is no doubt, of course, when considering a single foetus, that its growth pattern is heavily genetically determined. However, disagreement comes when we attempt to explain why two foetuses in two pregnant women grow with different rates. Is it due to different foetal genes, different maternal genes, different environmental influences or to different maternal constraining mechanisms?