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?

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In my opinion, there is nothing in the familial covariation of birth weight observed by Ounsted or others cited in the paper that necessitates a proposition of maternal constraint. A stronger correlation between maternal birth weight and offspring birth weight than between paternal birth weight and offspring birth weight can be explained by shared maternal genes. Ounsted allows for this possibility at the end of her paper, saying that: ‘transmission is effected through the female line, and may be attributable to the maternal genome’. Elsewhere, however, she regards the maternal constraining mechanism as: ‘an adaptive process which facilitates fairly fast changes in foetal growth rate as the conditions under which a population lives improve or deteriorate’. This almost Lamarckian idea might also pose dangers to a population if harsh environmental conditions in one generation would dictate the foetal growth pattern of the next generation. For birth weight, the effects of environmental factors appear to be surprisingly small, as summarized by Leon. He points out that there has hardly been any increase in mean birth weight over the past 100 years, that interventions to increase birth weight by nutritional supplementation have had little effect, and that the differences in birth weight between socio-economic groups are relatively small.

Although I disagree with Margaret Ounsted about the existence of a maternal constraining mechanism being set in utero, as I also did in 1986, her creative thinking on the basis of observed data is inspiring for workers doing animal experiments as well as for epidemiologists trying to sort out the many loose ends of birth weight associations. Clearly, we need to understand more of the causes of variability in birth weight before hypotheses are discarded.

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References