Long-term neurodevelopmental outcomes in small babies

Catherine Aiken

Abstract

The concept that health and disease outcomes in later life can be programmed during development in the womb is now well established through work in both human epidemiological studies and animal models. However clinicians are not often encouraged to consider this concept when caring for a baby who is at risk from a suboptimal intrauterine environment. Babies who are born at term below the 10th centile for gestational age are at increased risk of poor neurocognitive development later in childhood. The effect is consistent between studies that have examined development in infancy, mid-childhood, and through to adolescence. Impairment has been demonstrated in several different neurocognitive domains, including motor, vision, hearing and language development. Care must be taken however in the interpretation of the numerous studies in this area to carefully correct for all of the confounding socio-economic variables that can contribute both to restricted fetal growth and to poor childhood cognitive outcomes. When these are fully corrected for, an overall effect of poor intrauterine growth on neurodevelopment still remains, but the impact is less. Predicting a subset of small babies who are at particularly high risk for poor neurodevelopmental outcomes has as yet remained elusive, despite multiple attempts to use various individual growth parameters, Doppler ultrasound measurements and serum biomarkers to boost the predictive power.

Keywords neurodevelopment; intrauterine growth restriction; developmental programming; small-for-gestational age

Introduction

Much of antenatal care, and fetal medicine in particular, is focused on improving the long-term health and disease outcomes of babies that face sub-optimal early life environments. An entirely new area of scientific study, the field known as developmental programming, has sprung up in the last 30 years, dedicated to improving understanding of how intrauterine life can impact on offspring outcomes many years later. The aim this research is to uncover the mechanisms by which life in the womb affects the development of various organ systems, and in particular the developing brain.

In human pregnancies, unlike animal models, a suboptimal intrauterine environment can be hard to define and hard to detect in clinical practice. We lack well-validated tests to determine accurately which babies are struggling with a difficult early life environment. Thus, we are highly reliant on any factors that we are able to measure that may give us an insight into whether development in the womb is proceeding as expected. The key factors that are measurable in routine clinical practice are the growth of the fetus via ultrasound, the Doppler flow measurements in specific blood vessels, and maternal serum biomarkers (for example pregnancy-associated protein A). We know that these measures correlate to some degree with the chance of growth restriction and still-birth, and hence they are also correlated with a higher risk of iatrogenic preterm delivery. We know much less about whether these key measures, in particular fetal growth *in utero*, correlate with later neurodevelopmental outcomes in childhood.

In this review we critically examine the latest evidence linking fetal growth *in utero* with neurodevelopmental outcomes in childhood and beyond, and ask what extra information can be added by considering Doppler blood flow measurements or using other additional markers, for example maternal serum analytes, to refine our predictions. The main intervention we have at present to mitigate the detrimental effects of the intrauterine environment is to deliver the baby, and hence cut short the exposure. This strategy, however, exposes the baby to the risks associated with premature birth and hence may be counterproductive to long term neurodevelopment overall. There is thus an urgent need to be able to make an accurate risk assessment of both the short and long-term risks of the intrauterine environment to the developing fetal brain.

Impact of suboptimal growth on later neurodevelopmental outcomes

One of the inherent difficulties in critically appraising the evidence regarding outcomes for babies born at low birthweights is disentangling the impact of being small for gestational age (SGA) versus being growth-restricted *in utero* (IUGR). Traditional thinking about birth weight is that the mechanistic pathways that lead to infants being SGA (thought of as infants that are appropriately small and growing along their own centiles) are distinctly different from those that lead to IUGR (infants who may have failed to fulfil their growth potential). Coupled with this complexity is the confusion that arises from the many different definitions of small babies used in different research studies, for example birth weight below the 5th centile, birth weight below the 10th centile, or lowest decile of growth between subsequent ultrasound examinations. The multitude of different definitions makes direct comparisons between studies difficult and mainly precludes inferring other outcomes from available data. The other major problem that many studies examining the relationship between low birth weight and neurodevelopmental outcomes face is isolating the impact of intrauterine growth on fetal brain development from the multitude of other confounding factors. These include fetal genetic, karyotypic or structural anomalies, and maternal medical conditions. While these factors can be easily isolated in smaller studies, in larger studies that rely on national population databases they can be overlooked, or remain uncorrected for. Furthermore, the mechanism by which poor intrauterine growth arises may also influence the final outcome, and this is difficult to control for, even in well-characterised cohorts.

In this review, we will focus on singleton pregnancies, primarily because better quality evidence is available regarding

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outcomes. However, at least two recent studies have suggested that small for gestational age infants from multiple births may have significantly poorer reading skills in mid-childhood (5 years old) than their singleton counterparts.

Despite the methodological difficulties outlined, studies consistently show lower standardized neurodevelopmental scores in childhood when the birth weight is <10th centile, compared to children born appropriate for gestational age. Both neurological outcomes and cognitive outcomes are less good in early childhood in children with low birth weights. Neurodevelopment has been assessed using many different parameters in early childhood, and these vary depending on both the study design and the age of the children being assessed. Several studies have found that small for gestational age infants score worse on the Brunet-Lezine or Bayley Infant development test items, which should be administered by trained assessors only, in order to ensure valid and reproducible of the results. Similar results are obtained when parameters from the Newborn Behavioural Assessment Scale (NBAS) are used. As children become older, cognitive outcomes may become more easily objectively assessed with testing of IQ and other similar cognitive measures. Other domains such as motor skills, vision, and hearing can be assessed at earlier ages by relatively objective tests administered in research environments; again children who are smaller at birth consistently score more poorly across all domains in these assessments. Further studies have also used parent-reported behaviours, such as sleep and interaction with other children. These parameters present more difficulties in ensuring that there is consistent and unbiased reporting of the relevant outcome, particularly as they rely on retrospective recall of the parents, who may not be objective with regards to their views of their own child's behaviour. The very wide heterogeneity in outcomes studied is an important factor that makes systematic review difficult with regards to neurodevelopmental consequences of poor intrauterine growth.

A Japanese national cohort study, which was well controlled for social factors, found an increased incidence of parent-reported behavioural problems in mid-childhood and the overall mild impairment in learning, cognition and attention appears to persist into adolescence. However, population-based studies that demonstrate poorer attainment in testing for cognitive outcomes in low birth weight children must be very carefully controlled for socio-economic bias. When such adjustment is performed, a common finding is that although there is some independent effect of being born at low birth weight on educational attainment, there is a much stronger impact of low socio-economic status, with children of poorer families much more likely to experience both effects. Hence studies that do not correct adequately for social factors risk over-stating the influence of being born small on longer-term neurological outcomes. In general, studies have not specifically examined whether there may be differences in the effects of being born small for gestational age on male versus female infants. One study found that the effect was present only in female infants, but in the majority of studies the data were not stratified by fetal sex. However, as other developmentally programming adverse phenotypes (for example insulin sensitivity) are expressed differently in male versus female offspring, this is a specific question that merits further consideration.

Which intrauterine growth parameters best predict neurodevelopmental delay?

Accepting that children born at low birth weight (regardless of mechanism) have lower cognitive outcomes, the question then arises of whether or not we can refine predictions of neurodevelopmental delay based on specific growth parameters. Comparisons of different ultrasound and neonatal growth parameters may help to better define precisely which children within a cohort are at risk for later neurodevelopmental delay.

Head measurements

Although early studies in developmental programming in humans did imply that there might be an impact of head circumference growth on neurodevelopment and cognition in childhood, later evidence has failed to find such an effect. A large Spanish cohort examined the relationship between head circumference (measured both in utero and at birth), but found no relationship between these measurements and neuropsychological developmental in infancy (measured at 14 months). When cognitive outcomes are followed through to adolescence, head circumference parameters are no better than overall fetal growth in predicting adverse outcomes. Similarly, evidence suggests that the growth trajectory of the biparietal diameter in utero is not associated with childhood developmental delay. Hence, despite that fact that head measurements have been assumed to be more closely related to brain development than growth overall, they are not an improvement on overall feta growth as a predictor of long-term neurocognitive outcomes, and may offer less ability to differentiate the children at highest risk of these adverse outcomes.

Abdominal circumference

Abdominal circumference growth is a frequently measured parameter in studies of developmental programming in humans, as it is closely linked to childhood and later life metabolic and obesity outcomes. However few studies have specifically examined the link between growth of the abdominal circumference and childhood outcomes in neurodevelopment-related domains. At least one small study has shown that fetal and neonatal fat fold thickness is positively correlated with better cognition in infancy, but there is insufficient evidence at present to link the growth of the abdominal circumference to later neurocognitive outcomes.

Symmetric vs asymmetric IUGR

Some evidence suggests that IUGR which is not brain-sparing (i.e. where there is a reduced head circumference measured at birth) have poorer performance on cognitive and literacy testing on children with brain-sparing IUGR, i.e. head circumferences within the normal. However, other more recent studies in larger cohorts have found no difference between symmetric and asymmetric IUGR. Thus at present there is no consensus on whether the pattern of IUGR may robustly reflect the propensity to lower neurocognitive outcomes. A large well-phenotyped study in this area is required to resolve this question.

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