Cerebral Palsy and Intrauterine Growth

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Intrauterine growth is the increase over time in fetal size. Because growth velocity (eg, millimeters per week of gestation) is rarely used in pregnancy outcome studies, most of the discussion herein concerns the relative size at birth (eg, weight compared with that expected for gestational age) as an admittedly inadequate\cite{1} surrogate for intrauterine growth.

Infants who are somewhat heavier at birth than is average for their gestational age and gender are at the lowest risk of having cerebral palsy and the lowest risk of perinatal death\cite{2}. This optimum birth weight for best outcomes seems to be about one standard deviation (SD) heavier than the average birth weight for gestational age among healthy infants (Z score=+1). At all gestations, infants who are either smaller or larger than this optimum size have a progressively increased risk of cerebral palsy (Fig. 1)\cite{3}. These findings are based on a large collaborative study of 4307 singleton children with cerebral palsy recorded in population registers across Europe in which gestational ages were largely confirmed by ultrasound dating\cite{3}. They confirm and expand the results from several earlier cohort\cite{4,5} and case-control\cite{6–9} studies.

Several problems arise in the interpretation of the results from these and other reports of the relationship between cerebral palsy and the size-for-gestation.

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Work for this article was supported by European Commission fund DGXII-BIOMED2-Contrat NBMH4-983701.

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The influence of gestational age

Judgment of the relative size of infants at birth must take into account gestational age, because this age has a profound effect on the risk for cerebral palsy (Fig. 1) [10]. Low birth weight infants (<2500 g) may have elevated risks of cerebral palsy because they are (1) of optimum weight for gestation but are born too early (eg, preterm only), (2) light for gestational age but born at term (small for gestational age [SGA] only), (3) both preterm and light for gestational age, or (4) heavy for gestational age but delivered very early (one fifth of infants at greater than the 90th centile preterm weigh less than 2500 g).

Thus, significance of birth weight cannot be properly understood without also considering gestational duration [11]. Because many studies of the risk for cerebral palsy use birth weight alone unqualified by the gestational age at birth [12,13], the observed increase in the risk for cerebral palsy associated with low birth weight has dominated the results and often been attributed to intrauterine growth retardation [14]. In fact, one third of infants with cerebral palsy are of above average weight for gestational age, and more than two thirds are heavier than the most common criterion for SGA (10th centile weight for gestational duration) [3].

A related problem in studies of cerebral palsy and intrauterine growth is the bias introduced by the selection of study populations using birth weight cutoffs

Fig. 1. Prevalence of cerebral palsy by Z score of weight for gestation. Rates at size extremes for very preterm (<32 week) infants are likely to underestimate rates of fetal brain damage on account of very high neonatal mortality, which will be greatest in the most severely growth restricted. Z scores equate to centiles, for example, the 90th centile equals approximately 1.28 SDs above the mean fetal weight using fetal standards. (Adapted from Jarvis SN, Glinianaia SV, Torrioli M-G, et al. Cerebral palsy and intrauterine growth in single births: a European collaborative study. Lancet 2003; 362:1107; with permission.)
This practice results in an overrepresentation of small-for-dates infants because only they can satisfy the weight criterion at later gestations.

**Birth weight for gestational age**

When birth weight and gestational age data are both available, a more sophisticated account of relative size can be made using centile charts. Commonly, the attempt is made to define a “high-risk” subset of SGA and a similar high-risk group of large for gestational age (LGA) infants, leaving by exclusion a group who are considered an appropriate size for gestation (AGA). The actual centiles chosen to define these subgroups vary (eg, less than the 10th centile or less than the third centile for SGA). Regardless of the ones used, there are underlying weaknesses in this approach:

- The implications of falling beyond the cut point can be variable. For example, a group defined as below the 10th centile includes infants at 85% and 50% of their expected birth weight, a difference of more than 1 kg for an expected weight over 3 kg. The variability of implications would be compounded if inappropriate centile charts were used. Charts may be out of date. With the average weight of healthy infants at birth increasing by up to 50 g every 10 years, progressively fewer infants are qualifying as SGA as defined by old growth charts. The centile charts may also have insufficient adjustment for nonpathologic determinants of size for gestation, such as gender, parity, and maternal height.

- There is an assumption that SGA or LGA groups consist of “inappropriately” grown infants. For example, SGA infants are often considered to be pathologically small owing to some interference that restricts intrauterine growth rather than simply constitutionally small by virtue of genetic growth potential. Evidence of truly abnormal growth velocity among SGA infants is rarely available, and the identification of a pathologic subset based on abnormal body proportions is still uncertain. There are no discontinuities in risk profiles with changes in the size of infants at any gestation. On the contrary, the relationship of perinatal outcomes to relative birth weight for gestational age is usually continuous and often exponential.

- This continuous relationship can mean that the risk for a poor outcome changes progressively even within the range of what is considered an appropriate birth weight, for example, between the 10th and 90th centile. Because the great majority of births occur in this weight range, the relatively small changes in risks among them can contribute a large proportion of excess neonatal deaths and morbidity associated with variations in intrauterine growth. Many study samples are too small to categorize weight for gestation more precisely than as SGA, AGA, and LGA, and their results are too simplistic and may overestimate the minimum risk of cerebral palsy for the most optimally grown infants.
Suitable growth standards

The size of preterm infants should be compared with that expected of their “healthy” peers. It is now clear that infants born before 37 weeks’ gestation are not healthy in this sense but tend to be lighter[22] and slower growing[23] than fetuses of the same post conceptional age, presumably for reasons related to their preterm birth. Because conventional “neonatal” birth weight standards are based on the observed birth weights of infants born at different gestational ages, comparing the weight of preterm infants with cerebral palsy with these standards compares them with other preterm infants who themselves are more likely to be abnormally grown. To avoid this problem, the relative size of infants born before term should be judged using reference standards based on the intrauterine weight for gestational age (“fetal” standards) rather than birth weights. Such fetal standards are derived from ultrasound-based estimates of the weights of healthy infants in utero at known gestational ages[24,25]. The standards can be tailored to allow for other important fetal characteristics, such as sex, ethnicity, and parity, as well as maternal height[26].

Early studies of the risk for cerebral palsy in which the birth weight and gestational age of cases were known used neonatal weight standards to judge the relative size of cerebral palsy cases, often using gestation-of-delivery matched controls[6,8,27,28]. Typically, these studies reported that the risk for cerebral palsy was not elevated for very preterm SGA infants. The authors believe this is because the neonatal growth standards and the controls used were equally biased by the inclusion of an excess of abnormally light preterm infants. As seen in Fig. 1, when fetal growth standards are used, there is a significant elevation of the risk for cerebral palsy for very preterm SGA infants in a similar pattern to that which applies at term. The use of gestation-matched preterm controls can also make it impossible to disentangle the risk of cerebral palsy attributable to factors that are themselves associated with poor growth and preterm delivery. For instance, maternal pre-eclampsia, which is one of the most frequently occurring causes of growth restriction, can also be an indication for elective preterm birth. Although the risk for cerebral palsy in a SGA infant born very preterm owing to pre-eclampsia is lower than that in an infant born equally preterm for some other reason, it is considerably higher than the risk in the healthy term born infant without pre-eclampsia.

Appropriate denominators

Because cerebral palsy is usually not described until well after the neonatal period, the infants used to form the denominator for rates have survived at least the first month of life, the period of highest postnatal mortality. If neonatal deaths are included, they artifactually decrease the estimated rate, because they could not be included in the numerator even if they had cerebral damage that would have
resulted in cerebral palsy had they survived. Survival is strongly associated with size at birth [19]. Among very preterm infants who have the highest mortality, this can mean that the risk of cerebral palsy associated with small or very large size will be underestimated unless early deaths are excluded from the denominators [3].

Estimating the risk of cerebral palsy associated with variations in weight for gestation can be done without knowing the denominators, that is, the actual number of unaffected surviving infants in each weight-for-gestation category. Several case-control studies have calculated the odds ratios for cerebral palsy by birth weight for gestation [6–8,28] by using the distribution of birth weight for gestation in controls as an estimate of that in the source population from which the cases were drawn. If it is assumed that the weight distribution within each gestation week is gaussian (a reasonable assumption for term birth weights and for fetal weights), the use of controls is unnecessary. The distribution of weight for gestation of the source population will be adequately represented by the appropriate fetal growth standard. This method was used in the European study from which Fig. 1 is drawn [3]. It has the advantage of avoiding the bias to reduced intrauterine growth inherent in using preterm born controls.

Size versus growth/shape

Weight, at any gestation, is a snapshot of the infant’s size. When compared with normative growth charts, a single reading at the 10th centile, especially if the chosen standard is carefully adjusted for factors such as gender, parity, and ethnicity, merely indicates that among 100 infants of this gestational age in the standard population, 10% will be lighter. To assess whether growth is proceeding as expected, two or more readings at least a month apart are required [1]. The difference between these readings should ideally be compared with growth velocity standards (because normal growth velocity also shows constitutional variation between infants). In practice, there are few studies of the true relationship between intrauterine growth and perinatal outcomes. The authors are aware of only three such studies based on sequential ultrasound scanning of high-risk infants who were later followed up and among whom a number with decelerating growth had severe perinatal problems [29] or subsequent intellectual and behavioral impairments [30,31].

In the past, the timing of “growth failure” was imputed from the proportionality of the body parts at birth (ie, the shape of the baby) [32–34]. No one has comprehensively investigated fetal body shape ultrasonically, and doubt remains as to whether it is possible to characterize the growth history of infants in utero from the ratios of body measurements [35]. It is not clear that there is a single pattern of relative growth of different body parts applicable to all fetuses [36]. The discussion that follows is confined to studies of cerebral palsy in which intrauterine growth was judged by variations in size (ie, birth weight for ges-
tational age), and in which either preterm infants were excluded (ie, studies restricted to term births) or fetal growth standards were used to assess the appropriateness of size.

**Studies relating the size at birth to the risk for cerebral palsy in term infants**

The three case-control studies [6,8,9], two cohort studies [3,5], and one cross-sectional case study [4] exclude from their case material cerebral palsy of known postneonatal origin, whereas one study also excludes nonspastic cases [6]. Only some reports allow the illustration of the relationship among term infants in isolation. Fig. 2 combines the results from these studies [3,5,6,8] using a common metric for relative size—the Z score of birth weight for gestation—and a central reference value to calculate the change in risk associated with smaller or larger infants (ie, average birth weight=Z score of zero).

The results of these studies differing in time, geographic location, and methods are remarkably consistent. Nevertheless, there is a major difference in sample size, with the Western European study being the largest by orders of magnitude; therefore, that study must have the most precise estimates of relative odds. In agreement with the second largest study, the Western European study shows a clear minimum of risk at a Z score of +1 SD.

![Risk of cerebral palsy by Z score of weight for gestation (term births only). The studies, from Western Europe and the United States, exclude twins. The range of Z scores in the reference value varies between studies. A wide range (eg, 10th to 90th centiles in the United States) tends to depress the risks associated with extreme size categories. (Data from Refs. [3,5,6,8].)](image-url)
Does the relationship between cerebral palsy and intrauterine size vary by the type and severity of cerebral palsy or by characteristics of the fetus?

With the possible exception of preterm born dyskinetic cases, Figs. 3a and b show that the reversed J-shaped relationship with an optimum weight for gestational age at about +1 SD persists for every type of cerebral palsy irrespective of whether cases are born at term (≥37 completed weeks) or not. When all gestational ages are combined, these increases in risk to either side of optimum weight are statistically significant for each type separately. This finding broadly confirms the earlier observation of similar relationships in the two case-control studies of Swedish children with cerebral palsy that had sufficient numbers for analysis by type [8,28].

The severity of cerebral palsy as judged by difficulty in walking and intellectual deficit is related to the degree of “size” deviation (Fig. 4) [37]. Using the combined criterion of no independent walking and an Intelligence Quotient (IQ) of less than 50 to define severe cerebral palsy, the probability that cases of cerebral palsy will be in this severe group is significantly elevated to either side of the reference band. For a Z score less than 0.67, the odds ratio equals 1.36 and the 95% confidence interval (CI), 1.05 to 1.78; for a Z score of 1.28 or greater, the odds ratio equals 1.44 and the 95% CI, 1.02 to 2.05. The patterns of risk increase for more severe forms of cerebral palsy at nonoptimal sizes were seen in unilateral and bilateral spastic cases, for term and preterm births, and rather more obviously for males than females [37]. Not only the frequency of cerebral palsy
but also the relative severity of the cases increases away from the same optimum weight for gestational age.

The gender of the fetus also seems to influence the relationship between cerebral palsy and intrauterine growth [37]. Fig. 5 shows that at every Z score less than 0.67 (ie, below the 75th weight centile), the rate for males is statistically significantly greater than that for females. At a Z score of +1.3 (about the 90th centile),

![Graph showing differences in gender-specific prevalence of cerebral palsy by Z score of weight for gestation.](image)

Fig. 5. Differences in gender-specific prevalence of cerebral palsy by Z score of weight for gestation. Analysis using data set from the same study as in Figs. 1 and 3. Cases of each gender are related to their own fetal size standard. Z score of zero represents a heavier absolute male birth weight than that for females.

Fig. 4. Probability of more severe versus milder cerebral palsy by Z score of weight for gestation. Odds ratios (**P < .01) are by reference to Z score band 0.67 to <1.28 (approximately 75th to 90th fetal centiles). Analysis based on a subset of 3122 Western European cases with sufficient data to assign severity. (Data from Jarvis SN, Glinianaia SV, Arnaud C, et al. Case gender and severity in cerebral palsy varies with intrauterine growth. Arch Dis Child 2005;90:474–9.)
the difference disappears. Inspection of the statistically nonsignificant results from Western Australia [6] also suggests a higher risk in males who are SGA that disappears or even reverses for those heavier than the 90% weight for gestation centile.

What are the known “causes” of intrauterine growth disturbances? Are these same risk factors associated with cerebral palsy? If so, is growth disturbance part of the causal pathway?

Numerous studies have attempted to address these questions. The subject has been reviewed fully in two recent reports [14,38]. The authors have been able to find few new and relevant publications. Table 1 summarizes the results of studies that satisfy the inclusion criteria noted previously [3,6,8,14,20,38–46]. Many

<table>
<thead>
<tr>
<th>Factor (X) associated with aberrant size at birth</th>
<th>Is X a risk factor for cerebral palsy</th>
<th>Is risk of cerebral palsy with X primarily in LGA/SGA?</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital anomalies</td>
<td>Yes</td>
<td>No</td>
<td>[6,8]</td>
</tr>
<tr>
<td>TORCH infections</td>
<td>Yes</td>
<td>No evidence</td>
<td>[6,8]</td>
</tr>
<tr>
<td>Chromosomal defects</td>
<td>Yes</td>
<td>Not known</td>
<td>[14]</td>
</tr>
<tr>
<td>Twinning in 3rd trimester</td>
<td>Yes</td>
<td>Possibly in VPTB (LGA)</td>
<td>[38]</td>
</tr>
<tr>
<td>Placental and cord anomalies</td>
<td>Yes</td>
<td>No evidence</td>
<td>[6,39]</td>
</tr>
<tr>
<td>Pre-eclamptic toxemia</td>
<td>Yes</td>
<td>No</td>
<td>[6,40]</td>
</tr>
<tr>
<td>Bacterial genital tract infection</td>
<td>Yes</td>
<td>No evidence</td>
<td>[6]</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Yes</td>
<td>?No</td>
<td>[3,20]</td>
</tr>
<tr>
<td>Maternal starvation</td>
<td>No</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>Maternal alcohol abuse</td>
<td>Yes</td>
<td>Not known</td>
<td>[38]</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>NK</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Maternal lung/cyanotic heart disease</td>
<td>NK</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Maternal renal/malabsorption disease</td>
<td>NK</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Maternal diabetes (including gestational)</td>
<td>?Yes</td>
<td>Not known</td>
<td>[41–43]</td>
</tr>
<tr>
<td>Small maternal size (or low birth weight)</td>
<td>NK</td>
<td></td>
<td>[44,45]</td>
</tr>
<tr>
<td>Socioeconomic deprivation</td>
<td>Yes</td>
<td>No</td>
<td>[46]</td>
</tr>
<tr>
<td>Neonatal hypothermia</td>
<td>Yes</td>
<td>Little or no contribution</td>
<td>[6]</td>
</tr>
<tr>
<td>Neonatal hypoglycemia</td>
<td>Yes</td>
<td>Little or no contribution</td>
<td>[6]</td>
</tr>
<tr>
<td>Intrapartum stress</td>
<td>Yes</td>
<td>No</td>
<td>[38]</td>
</tr>
<tr>
<td>Clinical signs of birth asphyxia/hypoxia</td>
<td>Yes</td>
<td>No evidence</td>
<td>[6,8]</td>
</tr>
</tbody>
</table>

Abbreviations: TORCH, toxoplasmosis, other infection, rubella, cytomegalovirus, herpes; VPTB, very pre-term birth (<32 weeks gestational age).

a Indicates a risk factor also associated with large size at birth. Otherwise, these are all risk factors for small size.
studies are small and underpowered. The finding of “no evidence” in the third column indicates that no evidence of an association was found in a small study but does not rule out the possibility of a clinically significant association.

Several of the following causal mechanisms could result in a concentration of cerebral palsy at the extremes of growth, where → denotes causation, although mechanism B tends to be the default assumption in much of the literature with intrapartum events as the putative cause:

A. Risk factor → abnormal growth → cerebral palsy
B. Abnormal growth → risk factor → cerebral palsy
C. Risk factor → cerebral palsy → abnormal growth → abnormal growth
D. Risk factor → cerebral palsy

If the excess risk for cerebral palsy associated with a factor “X” (Table 1) was not concentrated at the growth extreme associated with X, this “cause” of cerebral palsy is likely to be operating independently of aberrant growth, suggesting mechanism D. For instance, although birth at less than 32 weeks’ gestation is associated with relatively small size at birth and also elevates the risk for cerebral palsy by 50 times when compared with the risk for births at 39 to 41 weeks, the latter applies more or less equally at each size centile (see Fig. 1). Even mechanism D may show a concentration of cerebral palsy at the extremes of growth if both causal paths (to abnormal growth and to cerebral palsy) were dose dependent, that is, the more severe the risk factor, the higher the risk of cerebral palsy and the more severe the degree of growth abnormality.

Despite a paucity of evidence, Table 1 indicates that the risk of cerebral palsy with factors associated with growth restriction is not concentrated in infants with growth anomaly. In fact, the risk of cerebral palsy is lower in SGA than in AGA infants exposed to twinning [38] or evidence of birth asphyxia [6,8]. This observation suggests an alternative causal mechanism. If growth restriction can represent a beneficial adaptive mechanism in the presence of a suboptimal exposure, the failure to make the appropriate adaptation may be responsible for the increase in risk of cerebral palsy associated with that exposure. Testing this hypothesis will require the ability to measure the severity of an exposure associated with growth anomaly independently of the degree of growth anomaly observed.

Implications

*Do studies of abnormal growth or size give information about the timing of any intrauterine events associated with cerebral palsy?*

If the increased risk of cerebral palsy associated with growth anomaly involved a single pathway, the striking pattern in Fig. 1 could be interpreted to
mean that the growth disturbance associated with cerebral palsy has already occurred by 28 weeks of pregnancy. Nevertheless, there are likely to be many possible routes to cerebral palsy associated with growth anomaly, summarized diagrammatically in mechanisms A to D. In mechanisms A and B, cerebral palsy is the direct or indirect consequence of the growth anomaly; therefore, the brain-damaging event would have to have occurred after the onset of growth deviation, neonatal hypoglycemia being a biologically plausible example. Because it takes weeks for growth deviation to become clinically discernible, mechanisms C and D would imply that the brain-damaging event occurred at least weeks before delivery.

Can abnormal growth, per se, cause cerebral palsy?

The real conundrum is whether cerebral palsy is a consequence (mechanisms A or B) or a cause (mechanism C) of growth deviation or simply an associated phenomenon (mechanism D). When the focus was entirely on the high risk for cerebral palsy in SGA infants, there was an understandable tendency to characterize the process as due to intrauterine growth restriction [14]. This causation was usually attributed to a constraint in fetal nutritional or oxygen supply with an effect on the fetal brain either directly from anoxia/hypoglycemia or indirectly by increased vulnerability to intrapartum stress.

The recognition that larger infants are at higher risk for cerebral palsy (and for other poor perinatal outcomes) has been mechanistically attributed to their disproportionate size in relation to the mother and to the increased risk of traumatic delivery. Nevertheless, as can be seen in Fig. 1, this excess risk applies equally to preterm infants who are overweight for their gestational age but actually of very small size relative to the mother. It has been proposed that the risk for relatively large infants could result from the association of cerebral palsy with specific, albeit, rare causes of megalencephaly [47]. The alternative attribution of high risk in this heavy infant group to maternal hyperglycemia and its degree of control does not seem to offer an obvious biologic route to fetal brain damage.

By way of contrast, the observation that the relationship of the risk for cerebral palsy with intrauterine size is continuous rather than confined to a clear “pathological” subset of SGA infants, and that this continuity extends beyond an optimum to encompass a progressive increase in the risk for abnormally large infants might suggest an alternative explanation. It does not seem implausible that the brain abnormalities underlying cerebral palsy occur before growth becomes disturbed. Several strong candidates for the causes of cerebral palsy, such as inherited clotting disorders [48], thyroid disturbance in the mother [49], vanishing twin [50] or twin/twin transfusions, and intrauterine infections [51], may exert their effects antenatally without any necessary pre-existing growth abnormality. As seen in Table 1, there is little evidence to refute this suggestion. On the contrary, once an insult to the developing brain or other organs has occurred, the control of fetal growth might be disturbed in a way that could err in
either direction (mechanism C). The subsequent observation that these growth-
disturbed infants have an excess of apparently noxious intrapartum factors in the chain of associated events may reflect their already compromised status [14].

This thesis that growth disturbances are a generic result of fetal insult is consistent with the almost identical association of intrauterine growth disturbances with perinatal mortality [19]. Furthermore, the type of cerebral palsy seems to have little influence on the relationship with size at birth.

Is there something about the intrauterine growth of male infants that might make them more susceptible to cerebral palsy?

If relative maturity of the fetus in utero is a form of “growth,” the short answer to this question might be that male infants are up to a month less mature at term (and presumably also proportionately less mature at earlier gestations) than their female counterparts [52,53]. This maturity difference is specifically true for cerebral anatomy (lateralization [54] and myelination [55]) and can be measured as differences of in utero behavioral adaptation to evoked responses [52]. Such immaturity might make male brains more vulnerable to insult at a variety of stages including intrapartum stressors.

Fig. 5 raises the intriguing possibility that the optimum size at birth for males is further from their population mean weight than is true for females. The rate of cerebral palsy in males even at the 90th to 97th weight centiles is lower (relative risk, 0.82; 95%CI, 0.67–1.01) than for males of “normal” birth weight (25th to 75th centiles), whereas for females, the reverse is true (Fig. 5). As male infants are significantly heavier than females, being further from optimum birth weight may arise owing to maternal constraint, a limit to intrauterine growth rate created by the limits of maternal resources which are reached earlier for the male infant than for the smaller female infant [44].

What are the implications for obstetricians?

The focus should arguably move to a detailed assessment of the health of fetuses in utero. Estimates of fetal size or preferably of the rate of change in fetal size may give important clues to the health of the fetus. If the brain damage associated with cerebral palsy precedes growth changes (mechanism C), recognition of growth restriction occurs too late for preventative intervention. With mechanism D, growth abnormality may be the first, albeit, crude signal that in utero pathology is occurring. This finding may indicate the need for further investigation with a view to potential in utero treatment (eg, of infections) or delivery in optimal circumstances. If the risk for cerebral palsy is elevated as a consequence of growth deviation (mechanisms A or B), underlying causes of growth abnormality may be pursued (placental compromise, gestational diabetes) or early delivery considered before fetal brain damage occurs.

These suggestions may be more pertinent in male infants, in twins, in situations in which a single measure of size is well away from the optimal for that
gestation, and when other known or significant risk factors for cerebral palsy are present. The latter include Leiden V consanguinity [48], a maternal history of thyroid disease [49], maternal infection [51], or familial twinning [50].

Whether any wider obstetric public health measures could be justified is open to question. There is little convincing evidence that intrauterine growth can be enhanced in developed countries by macronutrient supplementation during pregnancy, and, with a few exceptions (eg, folate levels), not enough is known about the role of micronutrition in pregnancy. A woman’s ability to sustain intrauterine growth seems to be determined by her socioeconomic circumstances and nutritional experience throughout childhood, mediated perhaps by her own birth weight and childhood growth [45,56]. More urgent public health interventions could be made in an attempt to increase the fitness of future rather than contemporary mothers.

What research is needed?

Research is needed to identify which causal mechanisms are responsible for the observed association between cerebral palsy and intrauterine growth anomaly. Cohorts of fetuses who have been subject to sequential (at least two) assessments of intrauterine size and with an accurately timed length of gestation should be observed in an attempt to characterize when in pregnancy the growth deviation associated with cerebral palsy or early brain lesions occurs. Because the outcome is rare, this would be easier in high-risk cohorts. There is some advantage to studying larger representative cohorts in which growth velocity patterns associated with optimal perinatal outcomes could be identified. The risks associated with observed fetal growth could be judged not in relation to a normative but to an optimal growth pattern. This investigation would be facilitated by the reliable prenatal identification of poor outcomes such as cerebral palsy, but this goal remains elusive at the population level.

Currently, most of the events that relate cerebral palsy to intrauterine growth are still hidden, although only a few centimeters away from view.

Acknowledgments

Figs. 1, 3–5, and associated analyses are based on data from the European Collaboration of Cerebral Palsy registers (SCPE). SCPE participants include C. Cans, J. Fauconnier (RHEOP, Grenoble, France), C. Arnaud (INSERM, Toulouse, France), J. Chalmers (ISDSHS, Edinburgh, United Kingdom), V. McManus (Lavannagh Centre, Cork, Ireland), J. Parkes, H. Dolk (Belfast, United Kingdom), G. Hagberg, B. Hagberg, P. Uvebrant (Gotenborg University, Gotenborg, Sweden), O. Hensey, V. Dowding (Central Remedial Clinic, Dublin, Ireland), S. Jarvis, A. Colver, (University of Newcastle, Newcastle, United Kingdom), A. Johnson, G. Surman (NPEU, Oxford, United Kingdom), I. Krägeloh-Mann, R. Michaelis
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