Annotation

Intrauterine growth retardation, general movements, and neurodevelopmental outcome: a review

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Intrauterine growth retardation (IUGR) due to placental dysfunction is a risk factor for an impaired neurodevelopmental outcome[2, 68]. This is the case particularly in growth-retarded foetuses whose conditions *in utero* are so compromised that they have to be delivered before term. In recent years, neonatal treatment and care have improved markedly, and this has led to increased chances of survival of very immature and extremely low-birthweight infants[46]. The optimal time to deliver IUGR infants remains difficult to assess. There is an obvious need for methods that accurately monitor foetal and neonatal condition, and it is important that the implications of these methods are evaluated for the neurodevelopmental outcomes of these infants. It is vitally important to be able to predict the outcome, whether it is normal or abnormal. A method that covers both aspects is the qualitative assessment of spontaneous motility of foetuses and newborn infants[49, 51].

This review summarizes several studies on the neurodevelopmental outcome of IUGR infants. It also investigates the relationship between the development of spontaneous motility early in life and obstetrical variables indicative of the foetal condition.

Neurodevelopmental outcome of IUGR infants

Although several studies have reported on the neurodevelopmental outcomes of IUGR infants, the results are conflicting. When reviewing these studies, a number of points that can explain the discrepancies among them should be considered (Table I). The most important point is the heterogeneity of the group of infants with growth retardation. Growth retardation is generally determined according to birthweight, so IUGR is considered more or less equivalent to small for gestational age (SGA). However, different criteria are used to define SGA. Neonatologists variously define SGA as a birthweight below the 2.3, 5th, or 10th centile on a birthweight versus gestational age curve. Particularly when the broadest criterion is applied, many of these infants would not qualify as IUGR at all: they just happen to fall into the lower range of the normal population distribution. In addition, some infants are born small because of an (undetected) chromosomal abnormality or dysmorphic syndrome. In addition, within the group of growth-restricted infants due to placental dysfunction, the onset and severity of the growth retardation add to the heterogeneity of the SGA group.

Another problem relates to heterogeneity of developmental tests used in the studies we reviewed. Neurodevelopmental assessment can be difficult. Gross effects can be easily quantified, whereas subtle or discrete lesions are more problematic. Some sophisticated tests may detect these subtle lesions, while others may overlook them. Furthermore, follow-ups of different durations, small sample sizes, inclusion of all gestational ages, or preterm or term SGA infants only, as well as specific characteristics of the control infants, could also explain the conflicting results.

Despite this, a number of conclusions can be drawn from the studies. Tables II, III, and IV show some characteristics and the main findings of case–control studies on neurodevelopmental outcomes published during the last 20 years. Table II presents studies that included infants of all gestational ages. Table III does the same for studies that included only term infants, and Table IV presents the findings on preterm

infants only. Generally speaking, there is an increased risk for mild neurodevelopmental abnormalities with cognitive disabilities and behavioural problems, more so than motor disturbances[82]. In addition, microcephaly at birth and a lack of catch up of head growth are related to an increased prevalence of neurodevelopmental abnormalities, especially in term infants with growth retardation[10, 66, 69]. This suggests that brain sparing is a relatively favourable feature in growth retardation. However, not all studies confirm this hypothesis. A recent study related foetal growth pattern in the third trimester to the neurodevelopmental outcome at 1 year of age[60]. Although the incidence of minor abnormalities was quite high (approximately one-third), no differences were found between foetuses that were already small and foetuses whose intrauterine growth was restricted.

The risk for major neurological abnormalities in infants with IUGR is less clear. Several studies reported a slightly increased prevalence of cerebral palsy (CP), especially in term infants with growth retardation[70, 71]. It is unclear if this finding also applies to preterm infants. Some studies did not find any difference[3, 31], while others reported an increased risk[27]. In comparison to term infants, the prevalence of CP is several times higher in preterm infants[28]; a slightly increased risk caused by growth retardation may be too small to be detected.

Table I: Reasons for conflicting results in studies on neurodevelopmental follow-up in infants with SGA/IUGR

Reasons for conflicting results
Definition of growth retardation (BW <10, <5, or <2.3 centile)
Inclusion or exclusion of infants with congenital anomalies
Inclusion of all gestational ages versus preterm or term infants only
Number of infants lost to follow-up (may exceed 50%)
Heterogeneous developmental tests to assess outcome
Different kinds of growth retardation (early or late onset)

SGA, small for gestational age; IUGR, interuterine growth retardation.

Evaluation of the foetal condition in case of IUGR

The evaluation of the foetal condition in growth-retarded foetuses is of the utmost importance to determine the optimal time for early delivery by Caesarean section, aiming at intact survival with a minimum of neurological sequelae. As yet, it remains uncertain when the growth-retarded foetus should be delivered. Various methods are used to monitor the foetal condition, e.g. foetal heart rate patterns[74], foetal biophysical profile scoring[39], and umbilical artery waveform patterns[15]. All these methods provide a good indication of perinatal complications, but the relevance for neurological sequelae remains unclear.

The foetal biophysical profile score consists of a combination of five items: foetal heart rate patterns, foetal breathing movements, foetal tone, foetal body movements, and amniotic fluid volume[39]. A score of 10 is obtained if all items are normal and 0 if all are abnormal. A clear correlation exists between perinatal complications, including mortality and a low biophysical profile score[37], particularly if the low score was caused by abnormal foetal heart rate patterns and decreased amniotic fluid volume[38, 57]. However, data on the relationship with neurological outcome are lacking.

Many studies have demonstrated that umbilical artery waveform patterns are impaired in pregnancies complicated by growth retardation[8, 21, 56]. A clear correlation was reported between abnormal umbilical artery waveform patterns and the risk of perinatal complications. An increased pulsatility index of the umbilical artery often precedes other signs of

Table II: Follow-up studies that included all gestational ages of infants with IUGR

Reference	*IUGR group characteristics*			*Control characteristics*	*Age at follow-up*	*Developmental tests*	*Results*
	N	*GA/BW*	*Centile*				
Berg (1988)[9]	602	All GA	<10th	BW >10th centile, N=4761	7 years	Neurological examination	No difference between groups in absence of perinatal stress
Tenovuo et al. (1988)[69]	519	All GA	<10th	BW >10th centile, term, N=3375	2 years	Denver Developmental Screening Test	IUGR infants had higher frequency of developmental delays compared to controls. Microcephaly at age 2 years associated with developmental abnormalities
Low et al. (1992)[36]	77	All GA	<10th	BW >10th centile, high risk group, N=141	9–11 years	Neurological exam, Bruininks–Oseretsky test, Wechsler Intelligence Scale for Children, Questionnaires (parents and teacher)	Overall 35% learning deficits associated with growth retardation and father's occupation
Fattal-Valeski et al.[22] (1999)	85	All GA	<5th	BW >10th centile, N=420	3 years	Neurodevelopmental Assessment Scale (NAS), Stanford–Binet test	IUGR infants had lower scores on NAS. IUGR infants with neonatal complications had lower scores than infants without complications

GA, gestational age; BW, birthweight.

foetal distress[58]. Absent or reversed end-diastolic velocities in the umbilical artery are associated with a perinatal mortality risk of up to 50%[43, 44]. However, only a few studies succeeded in finding a correlation between abnormal umbilical artery waveform patterns and later neurodevelopmental outcome[33, 34]. Moreover, although IUGR strongly correlates with placental markers indicating impaired utero–placental blood flow, no association was demonstrated between placental pathology and the neurodevelopmental outcome in the first year of life[26].

Recently, a method of recording foetal cerebral circulation was added to the diagnostic methods available for IUGR infants. It calculates the cerebro–placental ratio of blood flow which provides some measure of the degree of brain sparing. The cerebro–placental ratio was also impaired in growth-retarded foetuses, but again, no correlation was found between perinatal complications and neurodevelopmental outcome[16, 61], except, possibly, before 34 weeks' gestation[5]. Impairment may be a rather late sign: in a longitudinal study, the reduction in growth velocity preceded the changes observed in foetal circulation[29].

Other efforts to evaluate the condition of the foetus aim at a more accurate assessment of the neurological condition of growth-retarded foetuses and preterm infants. This approach

Table III: Studies on follow-up of term IUGR infants

Reference	*IUGR group characteristics*			*Control characteristics*	*Age at follow-up*	*Developmental tests*	*Results*
	N	*GA/BW*	*Centile*				
Low et al. (1982)[35]	76	Term born	<10th	BW >25th centile, N=88	5 years	Neurological examination, McCarthy motor scores, Wechsler Intelligence Scale for Children	No difference between groups
Villar et al. (1984)[73]	59	Term born	<10th	BW >10th centile, N=146	3 years	Battery of mental tests	IUGR infants had lower cognitive scores. Those with adequate ponderal indices had lowest scores
Berg (1989)[10]	467	Term born	<10th	BW >10th centile, N=4068	7 years	Neurological examination	IUGR infants with perinatal hypoxia-related factors had more neurological abnormalities but no difference between groups in absence of perinatal hypoxia-related factors. Microcephaly associated with increased risk of neurological abnormalities
Paz et al. (1995)[47]	64	Term born sgtns	<3rd	BW >3rd centile, N=1643	17 years	Neurological examination, Wechsler Adult Intelligence Scale	IUGR infants had increased risk for lower cognitive performance and schooling achievement
Pryor et al. (1995)[55]	91	Term born	<10th	BW >10th centile, N=946	13, 15, and 18 years	Wechsler Intelligence Scale for Children–Revised, Burt Reading Scores, Revised Problem Behaviour Checklist	IUGR infants had lower IQs at age 13 (IQ 101.2 vs 109.0). Parents of IUGR infants reported more behavioural problems at age 15y
Markestad et al. (1997)[40]	265	Term born	<15th	BW >15th centile, N=329	13 months	Bayley Scales of Infant Development	IUGR infants scored lower on mental scale (DQ 112 vs 116)
Strauss and Dietz (1998)[66]	2719	Term born	BW ≤2500g	BW >2500g, N=43 104	7 years	Wechsler Intelligence Scale, Bender–Gestalt test (visual–motor development)	IUGR infants had lower IQs (90.6 vs 96.8) compared to non-IUGR group, and lower Bender–Gestalt scores,
	220	Term born		non-IUGR siblings, N=220			No difference between IUGR infants and non-IUGR siblings. Siblings with IUGR and large deficit in head circumference had lower scores
Strauss (2000)[65]	1064	Term born	<5th	BW >5th centile, N=13 125	16 and 26 years	Vocabulary/spelling test at age 16y, Questionnaires (teacher and community health officer) on school performance, Questionnaire participants at age 26y	IUGR infants demonstrated small deficits in academic achievement at age 16 years. No difference between groups at 26 years

GA, gestational age; BW, birthweight; DQ, developmental quotient; sgtns, singletons.

Table IV: Studies on follow-up of preterm IUGR/SGA infants

Reference	*IUGR/SGA characteristics*			*Control characteristics*	*Age at follow-up*	*Developmental tests*	*Results*
	N	*GA/BW*	*Centile*				
Matilainen et al. (1987)[41]	23	<37 weeks	<2.3	BW >2.3 centile, PT-AGA N=48, term N=36	4 years	Neurodevelopmental Scoring Test, Psychological performance tests	IUGR infants had more moderate or high risk scores compared to both control groups. Abnormalities consisted of complex deviations of motor, visual, and perceptual functions
Hadders-Algra et al. (1988)[27]	27	<37 weeks	<10th	BW >10th centile, preterm AGA N=53, term AGA N=206. BW <10th centile, term GA N=166	6 years	Neurological examination, Questionnaire (parents and teacher)	Major and minor neurological abnormalities were more frequent in all three low-birthweight groups, especially in preterm SGA. Incidence of abnormalities: PT-SGA, major 15% minor 37% PT-AGA, major 4% minor 26% Term SGA, major 2% minor 24% Term AGA, major 1% minor 15%
Veelken et al. (1992)[72]	96	≤1500g	<10th	BW >10th centile, AGA N=275	18–20 months	Neurological examination, Griffiths developmental test	Incidence of CP was decreased in IUGR group compared to AGA infants (7% vs 17.5%, due to lower GA in AGA group). IUGR infants had higher frequency of minor neurological abnormalities (30% vs 15.3%)
Smedler et al. (1992)[64]	14	<37 weeks	<2.3	BW >10th centile, term born, matched for age, sex, socioeconomic background	8.7–11.2 years	Wechsler Intelligence Scale for Children, Bruininks–Oseretsky test, Halstead–Reitan neuropsychological battery, Southern California Tests of Sensory Integration	IUGR infants had lower scores on visuospatial ability, nonverbal reasoning, strategy formation, and gross motor coordination. More preterm IUGR infants had lowest scores
Sung et al. (1993)[67]	27	≤31 weeks	<10th	BW >10th centile, Matched for GA, AGA-GA, N=27, Matched for BW, AGA-BW, N=27	3 years	Neurological examination, McCarthy Scales of Children's Abilities, Peabody Picture Vocabulary Test	No difference for neurological outcome between IUGR group and AGA-GA matched group. Lower scores for developmental tests in IUGR group compared to AGA-GA matched group, but similar to AGA-BW matched group. Latter is due to lower GA of AGA-BW matched group
Wocadlo and Rieger (1994)[81]	18	<30 weeks	<10th	BW >10th centile, Matched for GA, sex, CLD and ultrasound findings, N=18	1 year	Bayley Scales of Infant Development or Griffiths Mental Development Scales	No difference between groups
McCarton et al. (1996)[42]	129	≤37 weeks, ≤2500g	<3rd centile	BW >3rd centile, AGA N=300	6 years	Neurological examination, Wechsler Intelligence Scale for Children–Revised	Increased risk for neurodevelopmental impairment in IUGR infants (IQ 85.4 vs 91.4). Higher incidence of neurological abnormalities (18% vs 10%, suspicious 11% vs 2%)

GA, gestational age; BW, birthweight; AGA, appropriate for gestational age; PT, preterm infants;CLD, chronic lung disease.

leads to a better understanding of CNS functioning in preterm infants with growth retardation, and is necessary to evaluate interventions. One of the new methods is the qualitative assessment of general movements (GMs) by videotape[49]. It proves to be a sensitive method for assessing the integrity of the CNS in early life. This method is non-intrusive, takes little time to carry out, and high interrater reliability scores are obtained[19]. Assessment can be repeated in the same individual so that a document of an individual's developmental course can be compiled. An added advantage is that the same qualitative criteria apply to both foetuses and preterm babies, as well as to infants during their first months of life.

Quantitative analysis of movement patterns

Prechtl's classification of spontaneous movement patterns led to a classification of the entire movement repertoire of the foetus and newborn infant[53, 54, 79]. The quantitative aspects of the movement patterns that were investigated included the emergence of rest–activity cycles as well as the rate of occurrence of several movement patterns. Both aspects were investigated under normal and compromised circumstances.

REST–ACTIVITY CYCLES AND BEHAVIOURAL STATES

During the second half of pregnancy, many movement patterns increasingly occur in clusters. This leads to rest–activity cycles that are clearly recognizable from about the 30th week of gestation onwards. In healthy preterm infants the rest–activity cycles can be identified at equivalent postmenstrual ages[18,53]. The rest–activity cycles precede the emergence of true behavioural states. In healthy foetuses, behavioural states are present from 36 to 38 weeks of gestation onwards[45,77]. In the way they are organized they are fully comparable to the behavioural states of term neonates. A number of researchers have demonstrated that the emergence of behavioural states is delayed in growth-retarded foetuses[4,76]. It is unknown if this is also the case in infants with growth retardation. The significance of these findings for the neurodevelopmental outcome remains unclear, because a delay in the development of behavioural states does not have a specific predictive value for the later outcome[50].

RATE OF OCCURRENCE OF DISTINCT MOVEMENT PATTERNS

A large range of intra- and interindividual variability exists in the rate of occurrence of all movement patterns throughout pregnancy[59, 78, 80]. This is also the case in healthy preterm infants[18, 53, 54]. The large variability in the quantitative data of spontaneous motility in uncompromised foetuses and in healthy preterm infants makes quantitative assessment an insensitive indicator of compromising conditions of the nervous system, a fact which has been demonstrated repeatedly. In growth-retarded foetuses a reduction in the quantity of general movements is a late sign of foetal deterioration[6, 7], since a reduction below the lower limit of normal occurs only in preterminal or terminal foetuses[58, 63]. In several studies on preterm infants, no difference in the quantity (frequency and duration) of various movement patterns was found between a high-risk group with brain lesions and subsequent disability, and a low-risk normally developing group [20, 23, 30, 54]. In preterm infants with growth retardation, the rate of occurrence of various movement patterns did not differ from that found in low-risk preterm infants[14], with the exception of the duration of GMs during the first week after birth, which was significantly lower in the infants with growth retardation.

Few correlations were found between the quantity of movement patterns after birth and obstetrical variables indicative of an impaired foetal condition. Only a reduction in foetal heart-rate variation was found to correlate slightly with an increased incidence of startles and twitches in the first week of life [14].

Therefore, it is clear that quantitative changes in motility are unsuitable markers of neurological dysfunction in foetuses and newborn infants. This is in striking contrast to the qualitative aspects of motility, which change dramatically in the case of brain damage or malformation[23, 24, 54, 75].

Table IV: Continued

Reference	*IUGR/SGA characteristics*			*Control characteristics*	*Age at follow-up*	*Developmental tests*	*Results*
	N	*GA/BW*	*Centile*				
Amin et al. (1997)[3]	52	≤1250g	<2.3	BW >2.3 centile, Matched for GA, AGA-GA, N=56, Matched for BW, AGA-BW, N=55	3 years	Neurological examination, Stanford–Binet Intelligence Scale	No differences between groups. Incidence of major neurodevelopmental abnormalities 15.4% vs 16.1% (GA-matched) and 16.4% (BW-matched). Persistence of microcephaly (in all groups) associated with adverse neurodevelopmental outcome
Kok et al. (1998)[31]	124	<32 weeks	<10th	BW >25th and <75th centile, N=410	5 and 9 years	5y: Neurological examination 9y: Questionnaire to parents (school performance)	At 5y: IUGR- infants had more gross motor dysfunction and MND (50% vs 36%); incidence of CP was identical. At 9y: 70–75% of IUGR infants needed special education vs 50% of control infants

GA, gestational age; BW, birthweight; AGA appropriate for gestational age; MND, minor neurological dysfunction.

Qualitative analysis of general movements

Of all the endogeneously generated movement patterns in foetuses and infants, GMs occur most frequently and they are very complex. They can be observed in foetuses as young as 9 weeks' postmenstrual age[79], and continue in a similar pattern after birth until about the end of the second month postterm. Normal GMs are characterized by a large variability in speed, amplitude, force, and intensity. The sequence of arm, leg, head, and trunk movements is complex, with rotations superimposed on flexion and extension, making the normal general movement look fluent and elegant[49]. In cases of brain abnormalities, such as cystic periventricular leukomalacia or large intracranial haemorrhages, the quality of the GMs is impaired: GMs appear monotonous with reduced complexity, variability, and fluency[23]. Three main types of abnormal GMs are described: (1) 'Poor repertoire GMs', when the sequence of successive movement components is monotonous, and arm, leg, trunk and head movements do not occur in the normal rich and complex sequence; (2) 'Cramped–synchronized GMs', when GMs appear rigid and stiff, lack the normal smooth and fluent character, and all limb and trunk muscles contract and relax almost simultaneously; (3) 'Chaotic GMs', when the movements of all limbs are of large amplitude and occur in a chaotic order without any fluency or smoothness[19, 52].

At about the end of the second month postterm, during the so-called major neural transformation[48], the GMs acquire a fidgety character. Fidgety GMs are circular movements of small amplitude, moderate speed, and variable acceleration of neck, trunk, and limbs in all directions[52]. They may be seen as early as 6 weeks postterm but usually occur around 9 weeks and remain present until 15 to 20 weeks. In preterm infants, this change in characteristics of spontaneous movements can be observed at about the same time if the infant's age is corrected for preterm birth. Abnormal movements at this age range are the complete absence of fidgety movements (however, other movements can occur), and abnormal fidgety movements, which resemble normal fidgety movements, but with exaggerated speed, amplitude and jerkiness[52]. The quality of fidgety movements has a high predictive power for the neurological outcome. Not only are abnormal or absent fidgety movements indicative of a poor outcome, but normal fidgety movements are an excellent predictor for a normal neurological outcome[52].

Relationship between quality of GMs, brain ultrasound findings, and neurodevelopmental outcome in IUGR

Several studies have investigated the quality of general movements in foetuses and infants with IUGR. Movement quality was found to be impaired in IUGR foetuses[6, 52]. Similar findings were reported in cross-sectional studies in preterm[25] and term[32] SGA infants. The developmental course of the quality of general movements in preterm IUGR infants has also been elucidated. A clear relationship exists between specific developmental trajectories of GM quality and the neurological outcome at 2 years of age[13]. In contrast, the neurological outcome is not correlated to brain ultrasound findings, obstetrical variables indicative of foetal distress, the degree of growth retardation, or the extent of brain sparing. Thus, the assessment of the quality of GMs in preterm SGA infants is a sensitive method with a high predictive value for the later outcome, as it is in preterm infants who are appropriate-for-gestational age (AGA)[1, 11, 23].

It appears that most IUGR infants have an abnormal quality of GMs during their preterm period, but the longitudinal approach reveals that the quality of GMs normalizes in the majority of the infants, at or after term age[13]. Some infants have consistently abnormal GMs, and this feature is predictive for an abnormal outcome. The quality of fidgety movements, in particular, is predictive of the final outcome. It must be noted that cramped–synchronized GMs, as an abnormal type of movement predictive for CP, occur rather late in infants with growth retardation, as compared to AGA infants[23]. Interestingly, a large proportion of infants with growth retardation who have abnormal GMs have normal findings on brain ultrasound scans[13]. This suggests that the chronically-reduced foetal supply of oxygen and nutrients may lead to a longer lasting, but often transient, brain dysfunction, which is not necessarily caused by haemorrhagic or hypoxic–ischaemic lesions detectable on ultrasound scans.

The qualitative assessment of GMs has proved its worth mainly in relation to the prediction of motor disorders. Future studies will need to elucidate whether the quality of GMs is also predictive of the cognitive disabilities and behavioural problems that are found more often in IUGR infants.

Relationship between quality of GMs and obstetric variables

Detailed analysis reveals several types of abnormal GMs in growth-retarded foetuses and infants. In two studies, a large proportion of foetuses and infants had 'slow motion' GMs[13, 62]. Obstetrical variables indicative of a compromised foetal condition were not related to this movement quality. It was suggested that a reduced amount of amniotic fluid directly affects the speed and amplitude of GMs[62]. Surprisingly, slow motion GMs also occurred in infants whose mothers had not received corticosteroids before birth[13]. The reason for this effect remains unclear. It could be due to a decreased incidence of neonatal respiratory morbidity, or direct neurological or metabolic effects that alter the character of the movements[12].

'Chaotic' GMs are also frequently observed in infants with growth retardation, but have not been reported in growth-retarded foetuses. In term SGA infants, the qualitative assessment of movement patterns reveals an increased incidence of jerky and tremulous movements[32]. In preterm SGA infants, the presence of this abnormal movement type is related to late foetal heart-rate decelerations and ischaemic alterations of the placenta[13]. This indicates that acute foetal deterioration, superimposed on chronic placental insufficiency, might be responsible for the occurrence of this movement type. The chaotic GMs in the latter study were not related to detectable brain lesions.

Conclusion

Recent studies have shown that the qualitative assessment of GMs is a powerful diagnostic method to evaluate brain dysfunction in preterm and term infants. Many infants with growth retardation have transiently abnormal GMs, indicating the importance of obtaining multiple observations. The quality of fidgety movements, in particular, is predictive for the neurodevelopmental outcome. It has been suggested that GM abnormalities at a young age are related to lesions of neural subsystems whose role in motor control ceases after 2 to 3 months[17]. These abnormalities may disappear if the new, posttransformation set of neural functions is not impaired. The assessment of developmental trajectories of GM quality

helps to select, at an early age, those infants who are at risk for developmental deficits and to provide surveillance and intervention on time.

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References

1. Albers S, Jorch G. (1994) Prognostic significance of spontaneous motility in very immature preterm infants under intensive care treatment. *Biology of the Neonate* **66:** 182–7.
2. Allen MC. (1984) Developmental outcome and follow-up of the small for gestational age infant. *Seminars in Perinatology* **8:** 123–56.
3. Amin H, Singhal N, Sauve RS. (1997) Impact of intrauterine growth restriction on neurodevelopmental and growth outcomes in very low birthweight infants. *Acta Paediatrica* **86:** 306–14.
4. Arduini D, Rizzo G, Caforio L, Boccolini MR, Romanini C, Mancuso S. (1989) Behavioural state transitions in healthy and growth retarded fetuses. *Early Human Development* **19:** 155–65.
5. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G. (1999) The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *American Journal of Obstetrics and Gynecology* **180:** 750–6.
6. Bekedam DJ, Visser GHA, de Vries JIP, Prechtl HFR. (1985) Motor behaviour in the growth retarded fetus. *Early Human Development* **12:** 155–65.
7. Bekedam DJ, Visser GHA, Mulder EJH, Poelmann-Weesjes G. (1987) Heart rate variation and movement incidence in growth-retarded fetuses: the significance of antenatal late heart rate decelerations. *American Journal of Obstetrics and Gynecology* **157:** 126–33.
8. Bekedam DJ, Visser GHA, van der Zee AG, Snijders RJM, Poelmann-Weesjes G. (1990) Abnormal velocity waveforms of the umbilical artery in growth retarded fetuses: relationship to antepartum late heart rate decelerations and outcome. *Early Human Development* **24:** 79–89.
9. Berg AT. (1988) Childhood neurological morbidity and its association with gestational age, intrauterine growth retardation and perinatal stress. *Paediatric and Perinatal Epidemiology* **2:** 229–38.
10. Berg AT. (1989) Indices of fetal growth-retardation, perinatal hypoxia-related factors and childhood neurological morbidity. *Early Human Development* **19:** 271–83.
11. Bos AF, Martijn A, Okken A, Prechtl HFR. (1998) Quality of general movements in preterm infants with transient periventricular echodensities. *Acta Paediatrica* **87:** 328–35.
12. Bos AF, Martijn A, van Asperen RM, Hadders-Algra M, Okken A, Prechtl HFR. (1998) Qualitative assessment of general movements in high risk preterm infants with chronic lung disease requiring dexamethasone therapy. *Journal of Pediatrics* **132:** 300–6.
13. Bos AF, van Loon AJ, Hadders-Algra M, Martijn A, Okken A, Prechtl HFR. (1997) Spontaneous motility in preterm, small for gestational age infants. II: Qualitative aspects. *Early Human Development* **50:** 131–47.
14. Bos AF, van Loon AJ, Martijn A, van Asperen RM, Okken A, Prechtl HFR. (1997) Spontaneous motility in preterm, small for gestational age infants. I: Quantitative aspects. *Early Human Development* **50:** 115–29.
15. Brar HB. (1988) The use of Doppler ultrasound to assess intrauterine growth retardation in the fetus. *Seminars in Perinatology* **12:** 40–51.
16. Chan FY, Pun TC, Lam P, Lam C, Lee CP, Lam YH. (1996) Fetal cerebral Doppler studies as a predictor of perinatal outcome and subsequent neurologic handicap. *Obstetrics and Gynecology* **87:** 981–8.
17. Cioni G, Ferrari F, Einspieler C, Paolicelli PB, Barbani T, Prechtl HFR. (1997) Comparison between observation of spontaneous movements and neurologic examination in preterm infants. *Journal of Pediatrics* **130:** 704–11.
18. Cioni G, Prechtl HFR. (1990) Preterm and early postterm motor behaviour in low-risk premature infants. *Early Human Development* **23:** 159–91.
19. Einspieler C, Prechtl HFR, Ferrari F, Cioni G, Bos AF. (1997) The qualitative assessment of general movements in preterm, term and young infants: review of the methodology. *Early Human Development* **50:** 47–60.
20. Erkinjuntti M. (1988) Body movements during sleep in healthy and neurologically damaged infants. *Early Human Development* **16:** 283–92.
21. van Eyck J, Wladimiroff JW, Noordam MJ, van den Wijngaard JA, Prechtl HFR. (1988) The blood flow velocity waveform in the fetal internal carotid and umbilical artery: its relation to fetal behavioural states in the growth retarded fetus at 37–38 weeks gestation. *British Journal of Obstetrics and Gynaecology* **95:** 473–7.
22. Fattal-Valevski A, Leitner Y, Kutai M, Tal PE, Tomer A, Lieberman D, Jaffa A, Many A, Harel S. (1999) Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. *Journal of Child Neurology* **14:** 724–7.
23. Ferrari F, Cioni G, Prechtl HFR. (1990) Qualitative changes of general movements in preterm infants with brain lesions. *Early Human Development* **23:** 193–231.
24. Ferrari F, Prechtl HFR, Cioni G, Roversi MF, Einspieler C, Gallo C, Paolicelli PB, Cavazzutti GB. (1997) Posture, spontaneous movements, and behavioural state organisation in infants affected by brain malformations. *Early Human Development* **50:** 87–113.
25. Geerdink JJ, Hopkins B. (1993) Effects of birthweight status and gestational age on the quality of general movements in preterm newborns. *Biology of the Neonate* **63:** 215–24.
26. Gray PH, O'Callaghan MJ, Harvey JM, Burke CJ, Payton DJ. (1999) Placental pathology and neurodevelopment of the infant with intrauterine growth restriction. *Developmental Medicine & Child Neurology* **41:** 16–20.
27. Hadders-Algra M, Huisjes HJ, Touwen BCL. (1988) Preterm or small-for-gestational-age infants. Neurological and behavioural development at the age of 6 years. *European Journal of Pediatrics* **147:** 460–7.
28. Hagberg B, Hagberg G, Olow I, van Wendt L. (1996) The changing panorama of cerebral palsy in Sweden. VII: Prevalence and origin in the birth year period 1987–90. *Acta Paediatrica* **85:** 954–60.
29. Harrington K, Thompson MO, Carpenter RG, Nguyen M, Campbell S. (1999) Doppler fetal circulation in pregnancies complicated by pre-eclampsia or delivery of a small for gestational age baby. II: Longitudinal analysis. *British Journal of Obstetrics and Gynaecology* **106:** 453–66.
30. Hines RB, Minde K, Marton P. (1980) Behavioral development of premature infants: an ethological approach. *Developmental Medicine & Child Neurology* **22:** 623–32.
31. Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. (1998) Outcome of very preterm small for gestational age infants: the first nine years of life. *British Journal of Obstetrics and Gynaecology* **105:** 162–8.
32. van Kranen-Mastenbroek VHJM, Kingma H, Caberg H, Ghys A, Blanco CE, Hasaart THM, Vles JSH. (1994) Quality of spontaneous general movements in full-term small for gestational age and appropriate for gestational age newborn infants. *Neuropediatrics* **25:** 145–53.
33. Ley D, Laurin J, Bjerre I, Marsal K. (1996) Abnormal fetal aortic velocity waveform and minor neurological dysfunction at 7 years of age. *Ultrasound in Obstetrics and Gynecology* **8:** 152–9.
34. Ley D, Tideman E, Laurin J, Bjerre I, Marsal K. (1996) Abnormal fetal aortic velocity waveform and intellectual function at 7 years of age. *Ultrasound in Obstetrics and Gynecology* **8:** 160–5.
35. Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J. (1982) Intrauterine growth retardation: a study of long-term morbidity. *American Journal of Obstetrics and Gynecology* **142:** 670–7.
36. Low JA, Handley-Derry MH, Burke SO, Peters RD, Pater EA, Killen HL, Derrick EJ. (1992) Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *American Journal of Obstetrics and Gynecology* **167:** 1499–505.
37. Manning FA, Harman CR, Morrison I, Menticoglou SM, Lange IR, Johnson JM. (1990) Fetal assessment based on fetal biophysical profile scoring. IV: An analysis of perinatal morbidity and mortality. *American Journal of Obstetrics and Gynecology* **162:** 703–9.
38. Manning FA, Morrison I, Harman CR, Menticoglou SM. (1990) The abnormal fetal biophysical profile score. V: Predictive accuracy according to score composition. *American Journal of Obstetrics and Gynecology* **162:** 918–27.

39. Manning FA, Platt LD, Sipos L. (1980) Antepartum fetal evaluation: development of a fetal biophysical profile. *American Journal of Obstetrics and Gynecology* **136:** 787–95.
40. Markestad T, Vik T, Ahlsten G, Gebre-Medhin M, Skjærven R, Jacobsen G, Hoffman HJ, Bakketeig LS. (1997) Small-for-gestational-age (SGA) infants born at term: growth and development during the first year of life. *Acta Obstetrica et Gynecologica Scandinavica* **76** (Suppl. 165)**:** 93–101.
41. Matilainen R, Heinonen K, Siren-Tiusanen H, Jokela V, Launiala K. (1987) Neurodevelopmental screening of in utero growth-retarded prematurely born children before school age. *European Journal of Pediatrics* **146:** 453–7.
42. McCarton CM, Wallace IF, Divon M, Vaughan HG Jr. (1996) Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. *Pediatrics* **98:** 1167–78.
43. McPharland P, Steel S, Pearce JM. (1990) The clinical implications of absent or reversed end-diastolic frequencies in umbilical artery flow velocity waveforms. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **37:** 15–23.
44. Montenegro N, Santos F, Tavares E, Matias A, Barros H, Leite LP. (1998) Outcome of 88 pregnancies with absent or reversed end-diastolic blood flow (ARED flow) in the umbilical arteries. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **79:** 43–6.
45. Nijhuis JG, Prechtl HFR, Martin CB Jr, Bots RS. (1982) Are there behavioural states in the human fetus? *Early Human Development* **6:** 177–95.
46. O'Shea TM, Preisser JS, Klinepeter KL, Dillard RG. (1998) Trends in mortality and cerebral palsy in a geographically based cohort of very low birth weight neonates born between 1982 to 1994. *Pediatrics* **101:** 642–7.
47. Paz I, Gale R, Laor A, Danon YL, Stevenson DK, Seidman DS. (1995) The cognitive outcome of full-term small for gestational age infants at late adolescence. *Obstetrics and Gynecology* **85:** 452–6.
48. Prechtl HFR, editor. (1984) *Continuity of Neural Functions from Prenatal to Postnatal Life. Clinics in Developmental Medicine No. 94.* London: Spastics International Medical Publications.
49. Prechtl HFR. (1990) Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. *Early Human Development* **23:** 151–8. (Editorial).
50. Prechtl HFR. (1992) Some remarks on the neonate. In: Nijhuis JG, editor. *Fetal Behaviour*. Oxford: Oxford University Press. p 65–72.
51. Prechtl HFR, Einspieler C. (1997) Is neurological assessment of the fetus possible? *European Journal of Obstetrics, Gynecology and Reproductive Biology* **75:** 81–4.
52. Prechtl HFR, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. (1997) An early marker for developing neurological deficits after perinatal brain lesions. *Lancet* **349:** 1361–3.
53. Prechtl HFR, Fargel JW, Weinmann HM, Bakker HH. (1979) Postures, motility and respiration of low-risk pre-term infants. *Developmental Medicine & Child Neurology* **21:** 3–27.
54. Prechtl HFR, Nolte R. (1984) Motor behaviour of preterm infants. In: Prechtl HFR, editor. *Continuity of Neural Functions from Prenatal to Postnatal Life. Clinics in Developmental Medicine No. 94*. London: Spastics International Medical Publications. p 79–92.
55. Pryor JE, Silva PA, Brooke M. (1995) Growth, development and behaviour in adolescents born small-for-gestational-age. *Journal of Paediatrics and Child Health* **31:** 403–7.
56. Reuwer PJHM, Sijmons EA, Rietman GW, van Tiel MWM, Bruinse HW. (1987) Intrauterine growth retardation: prediction of perinatal distress by Doppler ultrasound. *Lancet* **2:** 415–8.
57. Ribbert LSM, Nicolaides KH, Visser GHA. (1993) Prediction of fetal acidaemia in intrauterine growth retardation: comparison of quantified fetal activity with biophysical profile score. *British Journal of Obstetrics and Gynaecology* **100:** 653–6.
58. Ribbert LSM, Visser GHA, Mulder EJH, Zonneveld MF, Morssink LP. (1993) Changes with time in fetal heart rate variation, movement incidences and haemodynamics in intrauterine growth retarded fetuses: a longitudinal approach to the assessment of fetal well being. *Early Human Development* **31:** 195–208.
59. Roodenburg PJ, Wladimiroff JW, van Es A, Prechtl HFR. (1991) Classification and quantitative aspects of fetal movements during the second half of normal pregnancy. *Early Human Development* **25:** 19–35.
60. Roth S, Chang TC, Robson S, Spencer JA, Wyatt JS, Stewart AL. (1999) The neurodevelopmental outcome of term infants with different intrauterine growth characteristics. *Early Human Development* **55:** 39–50.
61. Scherjon SA, Oosting H, Smolders-de Haas H, Zondervan HA, Kok JH. (1998) Neurodevelopmental outcome at three years of age after fetal 'brain-sparing'. *Early Human Development* **52:** 67–79.
62. Sival DA, Visser GHA, Prechtl HFR. (1992) The effect of intrauterine growth retardation on the quality of general movements in the human fetus. *Early Human Development* **28:** 119–32.
63. Sival DA, Visser GHA, Prechtl HFR. (1992) The relationship between the quantity and quality of prenatal movements in pregnancies complicated by intrauterine growth retardation and premature rupture of the membranes. *Early Human Development* **30:** 193–209.
64. Smedler AC, Faxelius G, Bremme K, Lagerstrom M. (1992) Psychological development in children born with very low birth weight after severe intrauterine growth retardation: a 10-year follow-up study. *Acta Paediatrica* **81:** 197–203.
65. Strauss RS. (2000) Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British birth cohort. *Journal Americal Medical Association* **283:** 625–32.
66. Strauss RS, Dietz WH. (1998) Growth and development of term children born with low birth weight: effects of genetic and environmental factors. *Journal of Pediatrics* **133:** 67–72.
67. Sung IK, Vohr BR, Oh W. (1993) Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. *Journal of Pediatrics* **123:** 618–24.
68. Teberg AJ, Walther FJ, Pena IC. (1988) Mortality, morbidity, and outcome of the small-for-gestational age infant. *Seminars in Perinatology* **12:** 84–94.
69. Tenovuo A, Kero P, Korvenranta H, Piekkala P, Sillanpaa M, Erkkola R. (1988) Developmental outcome of 519 small-for-gestational age children at the age of two years. *Neuropediatrics* **19:** 41–5.
70. Topp M, Langhoff-Roos J, Uldall P, Kristensen J. (1996) Intrauterine growth and gestational age in preterm infants with cerebral palsy. *Early Human Development* **44:** 27–36.
71. Uvebrant P, Hagberg G. (1992) Intrauterine growth in children with cerebral palsy. *Acta Paediatrica* **81:** 407–12.
72. Veelken N, Stollhoff K, Claussen M. (1992) Development and perinatal risk factors of very low-birth-weight infants. Small versus appropriate for gestational age. *Neuropediatrics* **23:** 102–7.
73. Villar J, Smeriglio V, Martorell R, Brown CH, Klein RE. (1984) Heterogeneous growth and mental development of intrauterine growth-retarded infants during the first 3 years of life. *Pediatrics* **74:** 783–91.
74. Visser GHA, Huisjes HJ. (1977) Diagnostic value of the unstressed antepartum cardiotocogram. *British Journal of Obstetrics and Gynaecology* **84:** 321–6.
75. Visser GHA, Laurini RN, de Vries JIP, Bekedam DJ, Prechtl HFR. (1985) Abnormal motor behaviour in anencephalic fetuses. *Early Human Development* **12:** 173–82.
76. van Vliet MA, Martin CB Jr, Nijhuis JG, Prechtl HFR. (1985) Behavioural states in growth-retarded human fetuses. *Early Human Development* **12:** 183–97.
77. van Vliet MA, Martin CB Jr, Nijhuis JG, Prechtl HFR. (1985) Behavioural states in the fetuses of nulliparous women. *Early Human Development* **12:** 121–35.
78. de Vries JIP, Visser GHA, Mulder EJH, Prechtl HFR. (1987) Diurnal and other variations in fetal movement and heart rate patterns at 20–22 weeks. *Early Human Development* **15:** 333–48.
79. de Vries JIP, Visser GHA, Prechtl HFR. (1982) The emergence of fetal behaviour. I: Qualitative aspects. *Early Human Development* **7:** 301–22.
80. de Vries JIP, Visser GHA, Prechtl HFR. (1985) The emergence of fetal behaviour. II: Quantitative aspects. *Early Human Development* **12:** 99–120.
81. Wocadlo C, Rieger I. (1994) Developmental outcome at 12 months corrected age for infants born less than 30 weeks gestation: influence of reduced intrauterine and postnatal growth. *Early Human Development* **39:** 127–37.
82. Zubrick SR, Kurinczuk JJ, McDermott BMC, McKelvey RS, Silburn SR, Davies LS. (2000) Fetal growth and subsequent mental health problems in children aged 4 to 13 years. *Developmental Medicine & Child Neurology* **42:** 14–20.