DEVELOPMENTAL RISKS AND OUTCOME OF VERY LOW BIRTH WEIGHT INFANTS

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Introduction

"There can be little doubt that neonatal intensive care is social engineering" (1). Silverman's statement indicates why studies on the outcome of VLBW infants and on developmental risk factors are of outmost importance for all professionals dealing with prematurely born children.The following questions related to this topic are adressed in this article:

- Developmental outcome of VLBW infants
- Significance of prenatal, perinatal and postnatal risk factors
- Prognostic value of findings provided by imaging techniques

The data presented are based on the Zurich Follow-up Studies (2-10) and the literature.

Discussion

Developmental outcome. Preterm birth carries the risk of developmental disturbances in postnatal life, and this risk increases with decreasing gestational age (Figure 1 and 2).

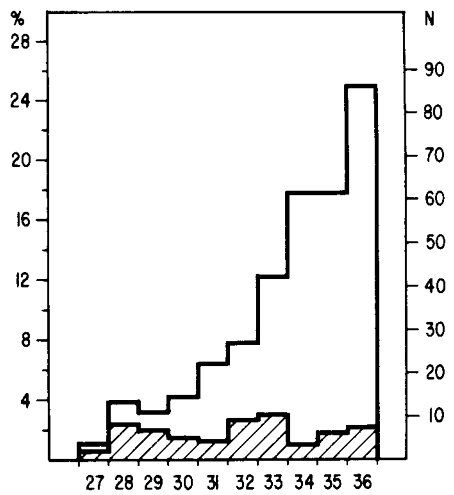

Figure 1
Low neurological optimality score in relation to gestational age in AGA-preterm infants. Solid line = distribution of gestational ages; hatched area = children with neurological optimality scores > 1 SD below mean value

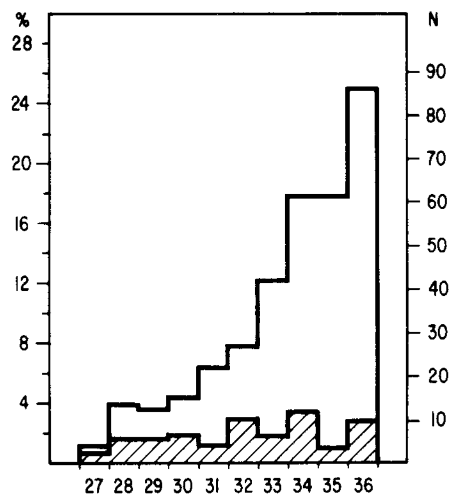

Figure 2
Low IQ in relation to gestational age in AGA-preterm infants. Solid line = distribution of gestational ages; hatched area = children with IQ > 1 SD below mean value (6)

There is a general agreement that infants born before 30 weeks of gestation have a less favourable development and are impaired neurologically more frequently than those born at a later gestational age.

The extent to which mental development and growth at age 2 in VLBW infants differ from those of healthy term children is illustrated in Table 1. With respect to mental

Table 1. Mental Development and Growth at Age 2 of Infants less than 1250 g at Birth (N = 67). Results Expressed as Standard Deviation Scores from the Mean Values of a Control Group of Healthy Term Children (10)

	Mean standard deviation score	p
Mental development		
Bayley mental score	- 1.10	< 0.001
Growth		
Weight	- 0.83	< 0.001
Length	- 0.47	< 0.01
Head circumference	- 0.61	< 0.001
Biparietal diameter	- 0.98	< 0.001
Fronto - occipital diameter	+ 0.36	< 0.05

development the preterm children performed at a significantly lower level than the term children. Their mean mental score was 1.1 SD below the mean of the control group. 16% of the preterm versus 3% of the term children achieved mental scores more than 2 standard deviations below the mean of the control group.

59% of the children were judged as neurologically normal. 33% of the children were diagnosed as having spastic cerebral palsy, 23% of mild, 5% of moderate and another 5% of severe degree; 8% of the children were ataxic-hypotonic.

Weight, length and head circumference were significantly lower in the preterm than in the term children. Their mean weight was 0.83 standard deviations (SD) below the mean weight of the control group. The corresponding value for their length was -0.47 SD and for their head circumference -0.61 SD. Head configuration was also significantly different, the biparietal diameter being smaller and the fronto-occipital diameter being larger in the preterm than in the term group.

How do these findings compare with those of previous studies? Differences in sample size, methodology and socio-demographic factors make comparisons with other studies difficult. Recently various authors have stressed the importance of using higher methodological standards in order to improve the reliability of follow-up studies. The essential requirements for follow-up studies are summarized in Table 2.

Table 2. Requirements for Follow-up Studies of Preterm Children (8)

Study design	**Methods**
Prospective versus retrospective	Test instruments
Longitudnal versus cross-sectional	Testing age corrected for prematurity
Duration of follow-up	Definition of impairments
Subjects	Recording of
Number of subjects	- risk factors
Age of testing	- socio-economic conditons
Selection bias	- ethnic, cultural factors
Mortality rate	Expertise of investigators
Definition of prematurity	Completeness of ascertainment
Appropriateness of birthweight	
Birth year	
Drop-out rate	
Control group	
Sex	

Significance of prenatal, perinatal and postnatal risk factors. Prenatal factors have received little attention in the past, presumably because their influence is underestimated, and because of methodological difficulties, for example, in defining minor congenital anomalies. In the Zurich Studies, at age of five years a

Table 3. Correlations between Developmental Outcome at Age 7, Minor Congenital Anomaly Score, Perinatal Optimality Score and Socio-economic Status in AGA-preterm Children (N=97) (10)

		Minor anomaly score	Perinatal optimality score	Socio-economic status
Neurological	M	- 0.55***	- 0.06	0.23
Optimality Score	F	- 0.40**	- 0.02	0.21
Intelligence	M	- 0.17	- 0.12	0.45***
Quotient	F	- 0.23	- 0.03	0.48***

** $p < 0.01$ *** $p < 0.001$

standardized examination for minor congenital anomalies was carried out and the presence or absence of 52 minor anomalies was noted. Minor congenital anomalies were observed more frequently in the preterm groups than in the term children ($p < 0.001$). There was also a significant negative correlation between the frequency of minor congenital anomalies and gestational age ($r = -0.33$, $p < 0.001$); thus the earlier a preterm infant was born the higher was the number of minor anomalies observed. The minor congenital anomaly score was significantly negatively correlated with the neurological score, and less so with measures of intellectual and language outcome (Table 3). One might speculate that the association between minor anomaly score and gestational age points to a prenatal factor, leading not only to deviations in the development of the central nervous system, but also to premature birth.

A large number of often severe perinatal complications appear to have only a minor influence on postnatal development (10). In the Zurich studies a modified version of Prechtls perinatal optimality score was used. This score includes 90 optimal conditions of pregnancy, birth and the neonatal period. In spite of the fact that the preterm infants were regarded as a high-risk group with respect to number of outborns and frequency of perinatal complications, the perinatal optimality scores revealed only a few inconsistently significant correlations with neurological and intellectual development (Table 3). These observations could lead one to conclude that perinatal complications play no role in future neurodevelopmental outcome. However, it is more likely that these results reflect the improved management of the preterm infant in the delivery room and in the nursery, thus diminishing the effects of perinatal complications on long-term outcome.

Birthweight, and more specifically gestational age, showed a consistent positive correlation with neurological, intellectual and language development. Allowing for confounding variables, such as the perinatal optimality score, statistical analysis revealed that before 40 weeks there may be postnatal factors (e.g. of metabolic origin, nutrition) which could have a negative impact on early extra-uterine brain development.

Recent research, in particular adoption studies, strongly suggest that effects of the socio-economic status (SES) relate to genetic endowment, as well as to the environment parents provide for their children. Correlating SES with intellectual and language outcome our studies revealed highly significant correlations between SES and intellectual outcome (Table 3).

Therefore, our results as well as those of other studies (11) strongly suggest that prenatal factors determine neonatal mortality and neurological morbidity to a much higher degree than adverse perinatal events, while socio-ecomonic conditions significantly affect language and cognitive development.

Prognostic value of findings provided by imaging techniques. Recent studies indicate that findings provided by ultrasound scanning, computerized tomography or nuclear magnetic resonance have greater predictive significance than any risk concepts used previously. The predictive value of ultrasound scanning is well demonstrated by the study of Graham et al (12) summarized in Table 4. The findings of cerebral ultrasound scanning during the neonatal period were related to presence or absence of cerebral palsy at 18 months. A consistently normal scan predicted normal outcome in 97% of cases and showed good specifity (83%) but poor sensitivity (45%). Infants with periventricular hemorrhage (PVH) alone and confined to the lateral ventricles were normal at follow-up. The presence of cysts accurately predicted abnormal outcome (94%) and was highly specific (96%).

Table 4. Prediction of Neurodevelopmental Outcome at 18 Months Based on Ultrasound -detected Abnormalities (12)

		PVH %	Prolonged flare %	Cysts %
Accuracy	True Positives+True Negatives	54	79	94
Sensivity	$\dfrac{\text{True Positives}}{\text{True Positives+False Negatives}}$	67	17	67
Specificity	$\dfrac{\text{True Negatives}}{\text{True Negatives+False Positives}}$	53	85	96
Positive predictive value	$\dfrac{\text{True Positives}}{\text{True Positives+False Positives}}$	11	9	62
Negative predictive value	$\dfrac{\text{True Negatives}}{\text{True Negatives+False Negatives}}$	95	92	97

Prolonged flare predicted adverse outcome but accuracy was less as compared to cystic periventricular leucomalacia. Positive predictive values were low, in particular for PVH and prolonged flares. Marked differences between studies indicate that the predictive validity of findings provided by imaging techniques strongly depends on the definition of the abnormalities disposed and the requirements outlined in Table 1.

A final note of caution: Predictive validity in most studies has been based on neurological outcome at an early age. To what extent intellectual, language and social development at schoolage can be predicted by imaging techniques remains to be shown.

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