Intrauterine malnutrition : neonatal and early childhood morbidity

INTRAUTERINE MALNUTRITION: NEONATAL AND EARLY CHILDHOOD MORBIDITY

PROEFSCHRIFT

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ABBREVIATIONS

A.G.A.	appropriate-for-gestational age
B.O.R.	behaviour observation report
B.S.Q.	behaviour screening questionnaire
D.F.	degrees of freedom
I.U.G.R.	intrauterine growth retardation
I.U.M.	intrauterine malnutrition
L	length
L.G.A.	large-for-gestational age
N.A.	not available
N.M.	neonatal mortality
N.S.	not significant
P	P-value
P.I.	ponderal index
P.N.M.	perinatal mortality
R.D.L.S.	Reynell Developmental Language Scales
S.D.	standard deviation
S.G.A.	small-for-gestational age
T.H.P.	total hydroxyproline
T.H.P./Cr. ratio	total hydroxyproline/creatinine ratio
W	weight

PREFACE

Intrauterine growth retardation is a major clinical entity in perinatal medicine. The magnitude of the problems of the small-for-gestational age (S.G.A.) infant is second only to prematurity as a cause of perinatal mortality and morbidity. The many unsolved questions surrounding this high risk group led to the publication of 3 dissertations in the Netherlands in the last 10 years. The first two studied the pathogenesis of neonatal hypoglycemia after intrauterine growth retardation: de Leeuw (1972) in small-for-gestational age newborn infants and Kollée (1980) in intrauterine growth-retarded rats. Lafeber (1981) studied intrauterine growth retardation in the guinea pig and investigated some of the consequences of this condition.

The 7 studies in this dissertation cover 3 main subjects: (1) the research for a biochemical parameter for prenatal diagnosis of intrauterine malnutrition in humans, (2) the use of a weight-length ratio (the ponderal index) as a measure to predict the neonatal morbidity of infants malnourished in utero, and (3) the growth and development in early childhood of infants affected by intrauterine malnutrition. These studies were performed in term S.G.A. infants who were underweight-for-length at birth. This subgroup of S.G.A. infants is usually known under the names 'intrauterine malnutrition', 'disproportionate intrauterine growth retardation', and 'subacute fetal distress' (and in the Netherlands as 'dysmaturity').

CHAPTER I: GENERAL INTRODUCTION

1.1 The small-for-gestational age infant

Low birthweight newborns do not constitute a homogeneous group since low birthweight may be the result of premature delivery, of intrauterine growth retardation, or of both these factors in combination (Warkany et al., 1961). Therefore these newborns must be classified in terms of both birthweight and gestational age. Those newborns born before the 37th week of gestation are called preterm infants whereas those having a relatively low birthweight for gestational age are called small-for-gestational age infants.

To be able to classify newborns by birthweight and gestational age reliable assessment of these parameters are critical. If the gestational age is not available (in case the mother is not sure of the date of her last menstrual period and/or her menstrual periods are irregular or she recently stopped the use of an oral contraceptive) the obstetrician can use physical examination early in gestation in combination with pregnancy tests and serial measurements of the biparietal diameter of the fetal skull by ultrasound (Campbell, 1969 and 1974; Queenan et al., 1976) to determine gestational age. The paediatrician can estimate the length of gestation to within plus or minus two weeks from the external physical characteristics (Farr et al., 1966; Usher et al., 1966) or from the neurological development (Saint-Anne Dargassies, 1962; Amiel-Tison, 1968) of the infants, or from a combination of the two (Dubowitz et al., 1970).

Lubchenco et al., (1963), compiled the first standards of intrauterine growth of (Caucasian) infants providing a valuable graphic method to classify low birthweight infants in terms of both birthweight and gestational age. This led to a classification of newborns in 9 categories (Table 1-1).

Table 1-1 Classification of newborns based on birthweight and gestational age

Birthweight	gestational age		
	< 37 weeks (less than 259 completed days)	37 - $41^{6}/7$ weeks (259 to 293 days)	> 42 weeks (294 days or more)
< 10th percentile	preterm S.G.A.*	term S.G.A.	post-term S.G.A.
10-90th percentile	preterm A.G.A.**	term A.G.A.	post-term A.G.A.
> 90th percentile	preterm L.G.A.***	term L.G.A.	post-term L.G.A.

* S.G.A.: small-for-gestational age
** A.G.A.: appropriate-for-gestational age
***L.G.A.: large-for-gestational age

Whereas there is international agreement on the definition of the preterm infant, no universally accepted definition of small-for-gestational age (S.G.A.) is available. Using an intrauterine growth curve arbitrary statistical limits are drawn to define S.G.A. Some authors (Lubchenco et al., 1963; Battaglia and Lubchenco, 1967; Babson et al., 1970; Davies et al., 1972) prefer to define S.G.A. as a birthweight at or below the 10th percentile for gestational age. Others (Gruenwald, 1963; Usher and McLean, 1969) advocate a birthweight more than 2 standard deviations below the mean for gestational age (corresponding to the third percentile on the intrauterine growth curve and a weight equivalent to 25% below the mean weight for gestational age). Still other authors (Thomson et al., 1968; Davies et al., 1979) prefer to use the 5th percentile as cut-off point. Of additional concern is that not all infants affected by intrauterine growth retardation will be included in a definition based on a relatively low

birthweight for gestational age: infants may manifest wasting at birth even though their weights do not fall below the normal for gestational age (Usher, 1970) and infants may be relatively underweight for gestational age when compared with their siblings (Turner, 1971).

Since the data of Lubchenco et al. (1963, 1966) of infants born at high altitude (Denver, Colorado) numerous tables and graphs of birthweight in relation to gestational age have become available from smaller and larger populations in Western countries. Well known examples are those of Gruenwald (1966) in Baltimore (U.S.A.), of Usher and McLean (1969) in Montreal (Canada), of Thomson et al. (1968) in Britain, of Babson et al. (1970) in Portland (U.S.A.), and of Kloosterman (1970) in Amsterdam (The Netherlands). An important problem in obtaining normative fetal growth data is that they are derived from cross-sectional measurements made on infants born in the latter half of pregnancy (with the exclusion of abnormal infants and multiple births). When delivery occurs before or after term, there may have been a physiologic handicap which may have adversely affected intrauterine growth. While these limitations must be borne in mind when interpreting intrauterine growth curves, there is no better method at the present time of deriving intrauterine curves of weight, length and head circumference in view of the inaccessibility of the fetus for study.

In the Netherlands recently a combination of the Usher-McLean (head circumference and length) and the Kloosterman intrauterine weight growth curves was chosen by the Dutch Neonatal Society as a reference for intrauterine growth (Versluys, 1980) to eradicate the confusion due to the use of a large number of different intrauterine growth curves in Dutch hospitals. In addition moderately S.G.A. was defined as a birthweight below the 10th percentile for gestational age and severely S.G.A. as a birthweight

below the 2.3 percentile for gestational age (Versluys, 1980).

1.2 Normal fetal growth

Two basic factors govern the velocity of fetal growth: the intrinsic growth potential of the fetus, which is genetically determined (Polani, 1974), and the growth support it receives via the mother and the placenta (Gruenwald, 1966). Animal data have shown that normal intrauterine weight growth of the fetus describes a sigmoid curve from conception till birth at term (Widdowson, 1970). Human fetal weight growth is almost linear from 28 to about 37-38 weeks, after which there is a gradual reduction in growth rate at term, with only minimal growth after term. This is

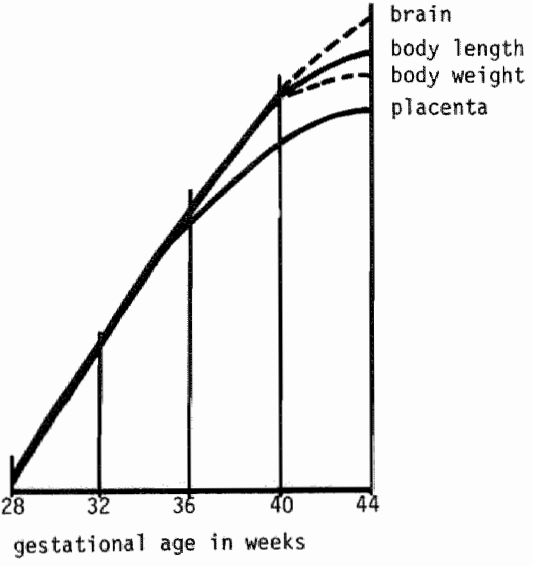

Fig. 1-2 Growth of brain, length, weight, and placenta post-term, adapted from Gruenwald (1974)

also true for other dimensions like length and head circumference (Usher and McLean, 1969). In post-term infants growth deceleration especially affects body weight, body length is less affected, whereas head size is least affected (Gruenwald, 1964 a) (fig. 1-2). The ponderal index, a weight-length ratio (100 x W/L^3) used to calculate the relative amount of soft tissue mass

present in an infant, shows a gradual increase from 30 through 37 weeks as the fetus accumulates (amongst others) subcutaneous fat (Widdowson, 1974 a). At term the ponderal index remains stable and is not affected by race, sex and parity. Post-term the ponderal index decreases as the increase in length is less reduced than the increase in weight at that time (Miller and Hassanein, 1971).

Probably some 40% of birthweight variation can be attributed to genetic variables whereas about 60% of the variation results from the environment in which the fetus grows, of which a greater part is dictated by maternal health and nutrition (Polani, 1974). Gruenwald (1966) suggested that if maternal growth support was unlimited, the growth rate of the fetus would proceed in a linear fashion towards term and post-term. There are two limiting factors which may influence late fetal growth to a large extent: (1)

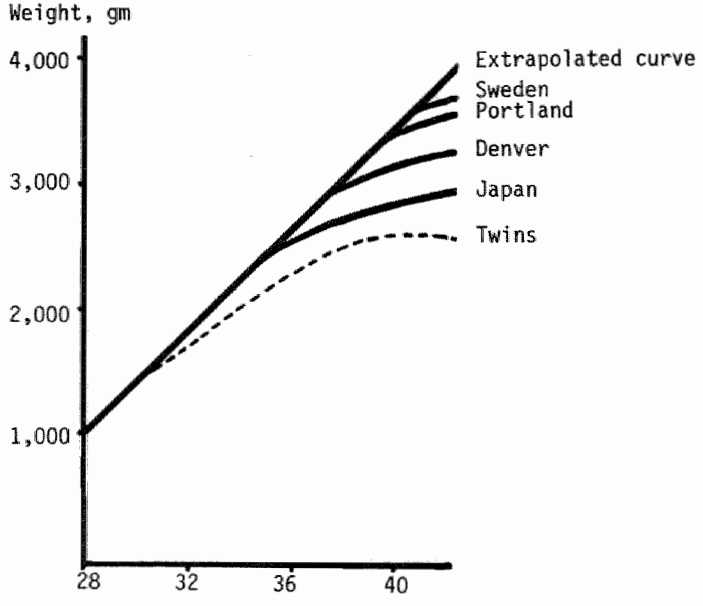

Fig. 1-3 Smoothed birth weight curves, suggesting that in each population departure from the straight line occurs when the supply line becomes insufficient to support the growth potential. Adapted from Gruenwald (1974).

the diminution of supplies from the mother to the fetoplacental unit because of a suboptimal utero-placental circulation, and (2) uterine constraints. This view is supported by the fact that the immediate postnatal growth of the fetus quickly accelerates to the pre-38 weeks growth rate once it has been released from the (normal) constraints of the uterine environment. From this evidence it would seem that ultimately birthweight is determined by the slope of the growth potential line, the gestational age, and the limiting factors occurring under normal circumstances (Ounsted and Ounsted, 1973; Dunn, 1981). The size that the human fetus could attain if the factor of maternal constraint was removed is a matter for speculation.

Gruenwald (1966 and 1974) demonstrated that all Western populations studied have similar, straight-line birthweight curves early in the third trimester, and depart from this straight line when the adequacy of the supply line to the fetus diminishes. This happens in each population at a time determined by the different limiting factors which are present (e.g. maternal nutritional status, race, and living at high altitude) (fig. 1-3). The lowest curve in figure 1-3 presents the growth of twins as an example of a group with a supply line which is limited more than it is in singletons. This figure also provides the intrauterine growth curves of Sweden, Portland, Denver, and Japan. In Sweden, the population with the largest babies, the deviation from the growth potential line occurs later in pregnancy than in a country with a shorter population like Japan. The Denver data (altitude 1,609 m.) describe an average U.S.A. population living at high altitude, the Portland curve was based on Caucasian infants living at sea level who were cared for by private physicians.

Growth at a cellular level has been investigated in animal studies (e.g. Winick and Noble, 1966; Hill, 1974; Widdowson, 1974

b). Three phases of development were proposed: first, a period when growth is entirely due to cell hyperplasia; second, a phase when growth is both by hyperplasia and hypertrophy; and lastly, a phase when growth is entirely by hypertrophy. Dobbing and Sands (1973) studied human abortuses, stillbirths, and neonatal deaths and described two phases of accelerated brain growth: one from 15 to 20 weeks of gestation, which is due to neuroblast proliferation, and the second from 25 weeks onwards which is the result of glial proliferation. Thus neuronal hyperplasia occurs during a phase of fetal growth without obvious limiting fetal growth factors. In addition to glial proliferation, many important changes are occurring in the late fetal brain such as myelination, dendritic arborisation and synapse formation which have profound influence on intellectual development. Though in man relatively little information is available, Dobbing and Sands (1970) found that cell hyperplasia ceased in the human brain during the second postnatal year.

Recently Dobbing and Sands challenged the entire 'cell number/ cell size' hypothesis by the demonstration that the three postulated phases of development do not occur in the human brain (Dobbing and Sands, 1981), nor in the 'non-neural' tissues like liver, kidney, heart, and gastrocnemius muscle (Sands et al., 1979). In all these tissues cell growth in size is apparently an early first event, coming to an end long before the process of cell division, which in turn continues as long as the growth of the tissue itself. This is exactly the opposite of the sequence originally proposed but it does account more satisfactorily for the failure of developing brain, as well as other tissues, to catch up following early nutritional or other growth restriction.

1.3 Factors limiting fetal growth

Reduced fetal growth rate can result from (1) a reduction of the

normal growth potential of the fetus and (2) from inadequate maternal support for fetal growth. Reduced growth potential can result from chromosomal abnormalities and genetic variabilities (Reisman, 1970; Polani, 1974), from congenital anomalies (Van den Berg and Yerushalmy, 1966), from intrauterine infections (Hughes, 1970), or from teratogenic agents.

Although chromosomal abnormalities are estimated to occur in about 6% of all conceptions (Wright, 1976) their numerical contribution to I.U.G.R. is limited (Keirse, 1981). The large majority of such pregnancies is lost before viability is reached and of the remainder about one third is accounted for by translocations which lead only rarely to a substantial alteration of growth. Most chromosomal abnormalities resulting in live birth, lead to a reduction of birthweight. Trisomy 21 (Down's syndrome), trisomy 18 (Edwards' syndrome), trisomy 13 (Patau's syndrome), Turner's syndrome (45,XO), and Klinefelter's syndrome (47, XXY) are well known examples (Polani, 1974). The effect of autosomal abnormalities is even more marked than that of anomalies of the sex chromosomes (Polani, 1974). The influence on weight of chromosomal abnormalities seems to be mediated through cellular changes and to be in essence the result of a prolongation or a shortening of specific phases of the cell cycle. The specificity and the direction of the effect depend on the nature of the chromosomal anomaly.

Intrauterine infections of viral origin will affect both fetus and placenta, but their negative effects on fetal growth depend on the timing of the intrauterine infection and will possibly to some extent be mediated by the effects of maternal illness (Coid, 1973). About 45% of infants with congenital rubella have a birthweight below the 5th percentile for gestational age (Turner, 1971), whereas 80% have an abnormally low birthweight when compared with the birthweight of their normal siblings (Turner,

1971). In I.U.G.R. due to rubella infection the liver and the spleen are rather large for bodyweight (because they are diseased) whereas the brain appears to be less protected than in many other causes of growth retardation (Naeye and Blanc, 1965). The rubella infection leads to a diminished cell multiplication, resulting in a numerical deficit of cells (Naeye and Blanc, 1965; Hughes, 1970).

Cytomegalovirus infection during pregnancy only leads in a minority of cases to I.U.G.R. (Hanshaw et al., 1973): if the infection is acquired around birth, weight may be normal, but if it is acquired much earlier the newborn is more likely to show growth retardation (Waterson, 1979). Congenital toxoplasmosis and syphilis may induce growth retardation, but their incidence is rather low and they do not invariably result in I.U.G.R. Though it is known that listeria infections may cause meningoencephalitis, and chorioamnionitis with preterm delivery and neonatal pneumonia, little is known about the influence of bacterial infections on the fetus.

High dosage ionizing radiation (Brent and Jensh, 1967), cytostatic drugs (Scott, 1977) and the administration of corticosteroids during pregnancy (Howard and Hill, 1979) may result in severe growth retardation. However in practice it is often very difficult to differentiate between the effects of the mentioned therapies and the effects of the maternal disease.

Excluding the indicated causes of I.U.G.R., the factors that may influence the adequacy of the supply line to the fetus (Gruenwald, 1964 b) can be roughly divided into 2 main groups: (1) placental factors, and (2) maternal factors.

It has always been tempting to attribute the birth of an unduly small infant to a functional inadequacy or insufficiency of the placenta. A critical survey of the possible causes of intrinsic placental inadequacy indicated that very few of these

can produce a degree of functional insufficiency sufficient to account for a low birthweight infant (Fox, 1976; Fox, 1981). There are four basic pathological mechanisms which can be held responsible: a) faulty placentation (esp. placenta circumvallata), b) a reduced mass of functioning villous tissue (esp. extensive infarction), c) abnormal villous development (esp. villous immaturity), and d) diffuse villous damage due to infection (malaria), aging, reduced fetal perfusion (haemangiomata of the placenta) and utero-placental ischaemia.

As intrinsic placental malformation is a rare cause of underweight at birth, a more important factor leading to a failure of fetal growth is an inadequate supply of nutrients by the mother to the fetoplacental unit because of compromised utero-placental exchange (Fox, 1981; O'Shaughnessy, 1981).

A great many maternal factors or conditions have been shown to be associated with I.U.G.R., for instance maternal nutrition (Naeye et al., 1973; Stein and Susser, 1976), smoking (Naeye, 1979; Murphy et al., 1980; Haworth et al., 1980 a and b; Bosley et al., 1981), alcohol and drug use (Redmond, 1979; De Lange, 1979), inadequate prenatal care (Miller and Hassanein, 1973), and low socio-economic class (Drillien, 1970). There appears to be a consensus of opinion that maternal vascular pathology, whether it is due to renal disease, essential hypertension, collagen-vascular disease or diabetes, is the single most common denominator in the causation of I.U.G.R. (Keirse, 1981). Dawes (1974) estimated maternal vascular disease to be responsible for approximately 35% of S.G.A. newborns.

Table 1-4 provides a picture of the many causes of retarded fetal growth. In the meantime it is still not really clear to what extent these conditions are responsible for I.U.G.R. General practice learns that a great number of specific fetal diseases (Usher, 1970), maternal factors (Miller and Hassanein, 1973;

Keirse, 1981) and placental lesions (Fox, 1976, 1981) are responsible for only a minority of the problem of reduced fetal growth. In the vast majority of S.G.A. infants no obvious cause can be identified which may explain their retarded growth (Dubowitz, 1974; Usher and McLean, 1974; Renfield, 1975).

Table 1-4 Causes of intrauterine growth retardation (adapted from Behrman, 1979; Fox, 1981, and Lafeber, 1981)

A. Fetal and feto-placental factors

- chromosomal disorders (e.g., autosomal trisomies)
- chronic fetal infection (e.g., rubella, cytomegalic inclusion disease)
- congenital anomalies (e.g., congenital heart disease)
- teratogenic agents (e.g., drugs, radiation injury)
- multiple gestation
- genetically determined variations

B. Maternal factors

- vascular disorders (e.g., toxaemia, eclampsia of pregnancy, hypertensive cardiovascular disease)
- hypoxia (e.g., high altitude, sickle cell anaemia)
- maternal addiction (e.g., heroin, alcohol, smoking)
- extreme malnutrition
- socio-economic factors
- small stature
- uterine constraint

C. Placental and materno-placental factors

- faulty placentation (e.g., placenta circumvallata)
- reduced mass of placental tissue (e.g., extensive infarction)
- abnormal villous development (e.g., villous immaturity)
- diffuse damage to the placental villi (e.g., infection)

1.4 Disproportionate intrauterine growth retardation as an expression of intrauterine malnutrition

Many descriptive names have been and are used to designate the growth retarded newborn: intrauterine growth retardation (Warkany et al., 1961; Lugo and Cassady, 1971), small-for-dates (Butler and Bonham, 1963), intrauterine malnutrition (Scott and Usher, 1966), light-for-dates (Davies et al., 1979), prenatal dystrophia (Thalhammer, 1964), pseudopremature infants (Söderling, 1953), chronic and subacute fetal distress (Gruenwald, 1963), fetal malnutrition (Miller and Hassanein, 1973), fetal dystrophy (Kloos and Vogel, 1974), dysmaturity (Sjöstedt et al., 1958; de Leeuw, 1973), and small-for-gestational age (Lubchenco et al., 1966). Among these the terms small-for-gestational age (S.G.A.) and small-for-dates are most commonly used at present.

The majority of intrauterine deprived infants are born at or near term (Usher and McLean, 1974; Neligan et al., 1976; Ounsted et al., 1981). In the Groningen Perinatal Project 7.5% of the S.G.A. infants (birthweight < 10th percentile) were born preterm (Jurgens-van der Zee et al., 1979). Ounsted et al. (1981) reported a percentage of 6.7% in S.G.A. infants (birthweight < 2 s.d. below the mean). If the nutrient supply to the fetus becomes insufficient to maintain normal fetal growth by the third trimester (there are few limiting factors prior to the 24 to 26th week of gestation other than those which the genetic program dictates; Warshaw, 1974), two main clinical patterns of intrauterine growth retardation may emerge, depending upon the duration, intensity and time of onset of the growth retardation (Gruenwald, 1963 and 1974): (1) Chronic fetal distress has a duration of months, often beginning early in the third trimester. At that time muscle mass is small and no sizable panniculus adiposus has yet developed. Thus, no 'wasting' can occur and external body proportions (weight, length, and head circumfer-

ence) are very similar to those of normally grown, preterm infants. These infants can be characterized by standard criteria of weight deficit, but not by such measures of body proportion as the ponderal index because they present proportionate intrauterine growth retardation. The maturation of these infants is very little affected and is advanced out of proportion to body weight as it remains related to gestational age. (2) Subacute

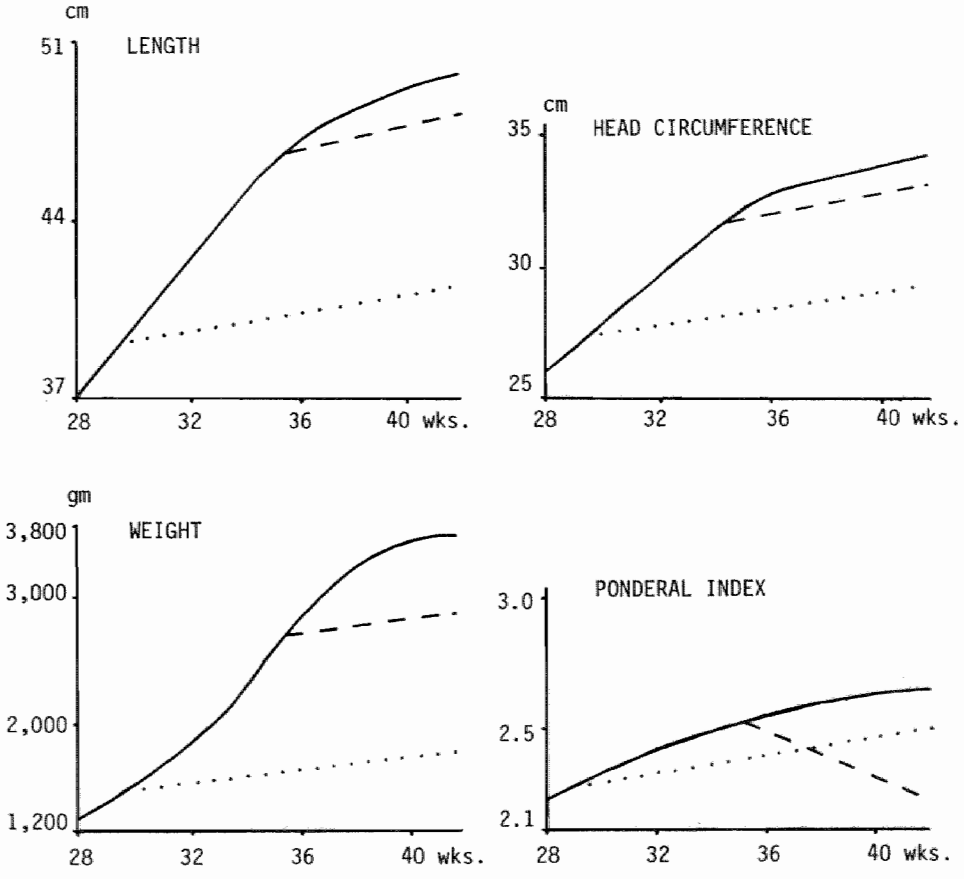

Fig. 1-5 50th Percentiles of normal intrauterine growth in weight, lenght, head circumference and ponderal index (weight-length ratio), adapted from Lubchenco et al., 1966. The 2 main patterns of intrauterine growth retardation (disproportionate I.U.G.R. = ------, and proportionate I.U.G.R. = ...) are inserted.

fetal distress, lasting for days or several weeks, usually affects fetuses near or past term who have grown to approximately full size for length and head circumference, but failed to develop a panniculus adiposus. This leads typically to a disproportion of (near) normal head circumference and body length and subnormal weight, with a reduced quantity of subcutaneous adipose tissue: disproportionate intrauterine growth retardation (fig. 1-5). The reduction in birthweight may not be sufficiently great to be detected using birthweight for gestational age as criterion. This clinical classification is (although useful) by no means infallible: there is a gradual overlap in the clinical characteristics of these two types of intrauterine growth retardation. But this classification is an attempt to determine the degree of I.U.G.R. so that subsequent studies will be able to define exactly the type of infant under discussion.

The ponderal index, (100 x weight/length^3), a weight-length ratio, was introduced by Rohrer (1921) for assessment of the nutritional status and for comparisons among groups of infants. This index has also been used to judge the nutritional status of newborns (Lubchenco et al., 1966; Miller and Hassanein, 1971; Gruenwald, 1974; Roord and Ramaekers, 1978). Between 30 and 40 weeks of gestational age, the 50th percentile of the ponderal index increases from 2.33 to 2.62 (Lubchenco et al., 1966), showing that the fetus becomes heavier for his length during the last trimester of pregnancy due to the accumulation amongst others of subcutaneous fat and muscle (Widdowson, 1974 a). In chronic fetal distress (proportionate I.U.G.R.) the index is low for gestational age, but is only slightly below the average when compared with that of infants whose weight is similar but appropriate for their gestational age. In subacute fetal distress (disproportionate I.U.G.R.) the index is considerably below normal no matter how it is considered (Gruenwald, 1974), see fig.

1-6. Especially at term the ponderal index provides valuable information about the nutritional status of the newborn: preterm infants have little subcutaneous fat and those with I.U.G.R. will have to be diagnosed by weight deficit. In clinical practice disproportionate I.U.G.R. is (depending on its severity) easily recognizable by the outward appearance of the newborn (Warshaw, 1979). The skin is ample and wrinkled with practically no subcutaneous fat. Widened skull sutures are present secondary to failure of bone growth, the head is relatively large. These newborns are usually alert, active, and seem hungry, although not necessarily from the first minutes of life. Meconium staining of the skin, nails, and umbilical cord is especially common in post-term infants.

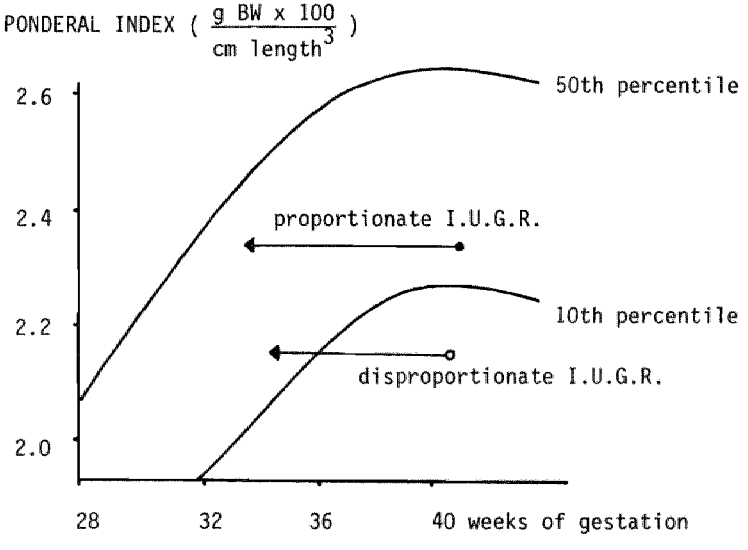

Fig. 1-6 Ponderal index of a representative case of disproportionate I.U.G.R. and proportionate I.U.G.R. The horizontal lines connect these with the points on which they would fall if their gestational age was commensurate with their actual birthweight (derived from Gruenwald, 1974).

Those term (S.G.A.) infants with clinically characteristic signs of intrauterine malnutrition and a relatively low ponderal index (to indicate underweight-for-length c.q. suboptimal nutritional status) constitute the study groups in this thesis. Several synonyms have been used to describe them (intrauterine malnutrition, subacute fetal distress, and disproportionate intrauterine growth retardation), but disproportionate intrauterine growth retardation was chosen in preference to any other synonym as the nutritional status was estimated in the ensuing studies by measuring and comparing weight and body length at birth.

1.5 The aims of the studies and selection criteria

Many of the early follow-up studies discussing the consequences of intrauterine deprivation are invalidated by the lack of adequate assessment of gestational age at birth and by the lack to define precisely the selection of the small-for-gestational age infants. One of the best-controlled studies has been that of Fitzhardinge and Steven (1972 a and b) who did a follow-up study of 96 term S.G.A. (birthweight more than 2 standard deviations below the mean) singleton infants born in Montreal in the years 1960-1966 who had no obvious cause for the growth retardation in the way of congenital malformations, infection, chromosomal abnormalities, and so on. This and other studies were performed before the introduction of modern intensive prenatal and postnatal care which eliminates many major risk factors for perinatal morbidity (for example early screening of blood glucose in combination with early and appropriate feeding lowered the incidence of neonatal hypoglycemia sharply). Furthermore these studies did not attempt to define the severity of the intrauterine growth retardation (chronic or subacute). So the question arose to what extent is past information still relevant when the 'black box' is opened at birth (when one is able to see the infant, to weigh it,

to measure it and to classify it) and the infant is subjected to the advanced perinatal care of the late seventies.

Aim I:

In the light of the above mentioned imperfections we became interested in the effect of intrauterine growth retardation on the long term morbidity of intrauterine malnourished infants who did fully benefit from modern perinatal care. To exclude morbidity due to the special problems of the preterm infant our subsequent studies were directed towards infants born at term. To define small-for-gestational age the 10th percentile of the Dutch weight-for-gestational age curves (allowing for sex and birth order) of Kloosterman (1970) was used. To avoid racial growth differences and the adverse effects of multiple pregnancy only Caucasian singletons were selected for further study. Infants with an obvious fetal disease (congenital malformations, infections, chromosomal anomalies) leading to growth retardation in utero and infants who were genetically small were excluded from the studies*. To eliminate the adverse effects of additional perinatal problems (like artificial delivery, asphyxia, acidosis, hypoglycemia, hyperviscosity, hyperbilirubinemia, hypothermia, and respiratory difficulties) on long term morbidity, only infants who were free from the mentioned factors were investigated. Ultimately the 10th percentile for gestational age of the ponderal index was used to select especially those term Caucasian singleton S.G.A. infants without fetal diseases who were underweight-for-length at birth (or in other words demonstrated sub-

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*The genetically small infants were identified by adjustment of their birthweight for maternal size according to Thomson et al., 1968; furthermore the ponderal index of these infants is (near) normal as both weight and length are small for gestational age.

acute fetal distress = disproportionate intrauterine growth retardation). Using these criteria several studies were performed with the ultimate aim to establish the early childhood morbidity of disproportionally grown term S.G.A. infants without fetal and neonatal diseases. Physical growth and developmental aspects were considered in a prospective study of 25 infants born in 1975-1976. These investigations were also performed in appropriate controls (term A.G.A. infants who were free from perinatal morbidity) carefully matched for age, sex, birth rank, and social class. At the age of three years (1979) growth was assessed by evaluating weight, length, head circumference, skinfold, and skeletal maturity. The results of this study have been described in publications IV and V. Development was assessed by testing behaviour, neurological and language development, all parameters of higher cerebral functions. Publications VI and VII describe the results of the developmental aspects of disproportionate intrauterine growth retardation.

Aim II:

In 1978/1979 we investigated the use of the excretion of hydroxyproline in the first urine as a biochemical index of the duration and severity of intrauterine malnutrition of term infants. This investigation (publication I) was undertaken in the light of the conflicting results about this subject presented by different authors in the last decade (see 2.1). The ponderal index was in this study used to quantify intrauterine malnutrition as the participating newborns ranged from normally grown infants to infants severely malnourished in utero.

Aim III:

More recently (1979-1981) we studied the incidence of disproportionate intrauterine growth retardation at term and the incidence of several neonatal problems among disproportionally (subacute

fetal distress) and proportionally (chronic fetal distress) grown term S.G.A. infants. In these papers (publications II and III) the ponderal index was again used as a measure of the nutritional status at birth. The aim of these studies was to test if disproportionally grown term S.G.A. infants are more liable to neonatal complications than proportionally grown term S.G.A. infants, a feature regularly observed in daily clinical practice. Those complications which are easy to define and to quantify and which are clinically relevant (asphyxia, acidosis, hypothermia, hypoglycemia, hyperviscosity, hyperbilirubinemia), were therefore considered in relation to birthweight and to ponderal index.

CHAPTER II: INTRODUCTION TO AND DISCUSSION OF THE PRESENTED STUDIES

2.1 Hydroxyproline, a biochemical parameter for the (prenatal) diagnosis of intrauterine malnutrition?

Although anthropometric values like weight, length, head circumference, and skinfold thickness are useful parameters to diagnose the severity of intrauterine malnutrition at birth, it remains difficult to assess the duration of the intrauterine growth retardation using these parameters. Several studies (Scott and Usher, 1964; Finnström, 1971; Pryse-Davies et al., 1974, Sénécal et al., 1977; Roord et al., 1978) have demonstrated that the ossification of epiphyseal centres (skeletal maturity) is markedly delayed when the fetus is malnourished in utero. Roord and Ramaekers (1978) showed that the severity of intrauterine malnutrition can be quantified by calculating the difference between the actual ponderal index ($100 \times W/L^3$) and the ponderal index of 'normally' grown infants (arbitrarily P50 values) and that this deviation from 'normal' correlated in a highly significant manner with skinfold measurements as a measure of the nutritional status at birth. Except that the ponderal index proved to be a valuable parameter of the nutritional status of the newborn, another study by Roord et al. (1978) established a close relation between skeletal retardation and negative deviation of the ponderal index from normal.

Interested in the possibility of employing a biochemical test for detecting the nutritional status in utero, the described link between anthropometric values (especially the ponderal index) and skeletal maturity at birth contained a possibility for further studies. As a major part (more than 50%) of the total body collagen stores is present in bone and as the rate of turnover of

collagen in bone is high (Neuberger and Slack, 1953), the metabolism of collagen might provide a parameter to quantify intrauterine growth retardation biochemically. The occurrence of hydroxyproline in collagen is of special interest since this amino-acid has been found only in collagen. Most of the hydroxyproline is present in collagens as the trans-4-isomer, but all known collagens also contain a small amount of trans-3-hydroxyproline, and basement membrane collagens are relatively rich in 3-hydroxyproline. Its unique place in collagen metabolism is based on the essential role of the hydroxylgroup of hydroxyproline in stabilizing the triple helix of collagen (Prockop et al., 1979). Although the bulk of body collagen is remarkably stable, a fraction of the collagen in all tissues is continually degraded and replaced, even in old age. Such changes in overall collagen metabolism can be conveniently followed by assaying excretion of hydroxyproline in urine (Kivirikko, 1973), as excretion of this substance is largely caused by collagen degradation and as collagen degradation parallels the decrease in collagen synthesis that occurs with age. Further studies on hydroxyproline have been facilitated by the fact that neither free hydroxyproline nor the hydroxyproline - containing polypeptides produced during the normal in-vivo degradation of collagen and excreted in the urine, are re-incorporated into collagen (Stetten, 1949; Bensusan and Klein, 1965). By means of tracer experiments it has been demonstrated that only free proline is built into the polypeptide chain of the collagen precursor protocollagen, and that subsequently part of these proline residues are hydroxylated to hydroxyproline (Udenfriend, 1966; Prockop et al., 1979). In normal children and in adults, about 95% of hydroxyproline (HP) is excreted in the peptide-bound form, and this fraction accounts for most of the increased hydroxyproline excretion rates occurring in various diseases affecting collagen metabolism, and

conditions associated with depressed, or increased rate of growth (Jasĭn et al., 1962 a, b; Smiley and Ziff, 1962; Picon et al., 1965; Graf and Vest, 1971; Wharton et al., 1972 and 1973; Cabacungan et al., 1973; Chandraschkharan and Candlisch, 1973; Teller et al., 1973; Futrell et al., 1975; Laitinen, 1975; Edwards et al., 1976).

Figure 2-1 shows the total hydroxyproline/creatinine (THP/Cr) ratio in urines from children of different ages (according to

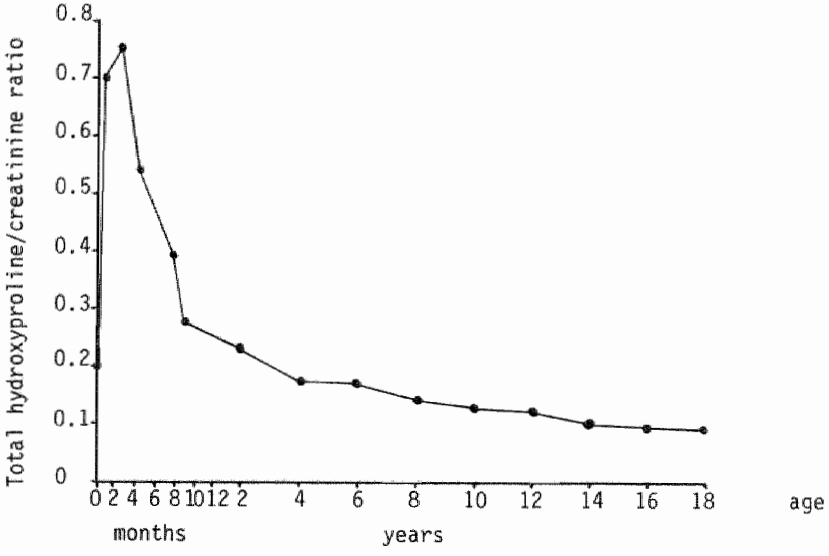

Fig. 2-1 Total hydroxyproline (mmol/l)/creatinine (mmol/l) ratio in urine collected from normal children of 0 to 18 years of age (adapted from Graf and Vest, 1971).

Graf and Vest, 1971), about equal figures were presented by Wharton et al. (1972). Both studies demonstrate that after birth the ratio rises rapidly (creatinine excretion remains stable and hydroxyproline excretion rises), reaching a peak towards the end of the neonatal period. Thereafter it falls progressively with increasing age, the reason is that creatinine excretion rises with increasing size and musculature whilst hydroxyproline excretion shows much less marked changes with increasing age. In fact

during the first year of life the amount of hydroxyproline excreted per kg bodyweight is larger than after infancy. The increased rate of growth during puberty manifests itself in a rapid increase of the absolute value of the excreted hydroxyproline from the age of 9 years onwards (fig. 2-2). This increase parallels the gain in weight and height (in girls earlier than in boys). At the same time creatinine and nitrogen excretion rise

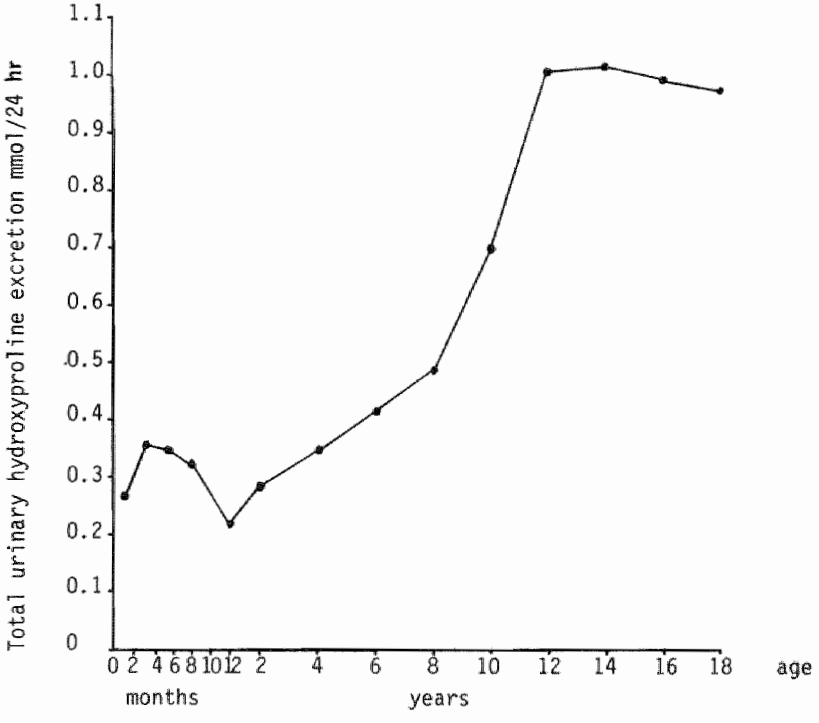

Fig. 2-2 Total hydroxyproline excretion (mmol/24 hr) in urine collected from normal children of 0 to 18 years of age (adapted from Graf and Vest, 1971).

and as a result the THP/Cr ratio continues to fall during puberty. Whereas a rapid growth rate results (except during puberty) in an increased THP/Cr ratio, malnutrition leads to a decreased ratio (Picon, 1965; Whitehead, 1965 and 1969; Howells et al., 1967; Chandraschkharan and Candlish, 1973) as has been shown in different studies from developing countries. The study

of Howells et al. (1967) in Kampala (Uganda) demonstrated that the total hydroxyproline/creatinine ratio in malnourished children on admission (0.18 ± 0.10 mmol) was significantly lower than in normal children (0.32 ± 0.12). After treatment there was a significant rise in the ratio to almost normal levels (0.29 ± 0.14 on discharge). Picon et al. (1965) also established a decreased hydroxyproline excretion in malnourished children in Jamaica as the result of a reduction in the turnover rate of collagen. Creatinine excretion followed a similar pattern, but the decrease and the increase during treatment were not so great.

The neonatal findings in S.G.A. infants are really confusing (table 2-3) when compared with those obtained during malnutrition in infancy and childhood. Younoszai and Haworth (1968) investigated the daily urinary excretion of total hydroxyproline in normal term, preterm and S.G.A. (birthweight < 10th percentile for gestational age) infants on the 1st and 3rd day of extrauterine life. On the first day after birth S.G.A. and normal infants excreted comparable amounts of total hydroxyproline. Though on the 3rd day all infants excreted significantly higher amounts of hydroxyproline than on the 1st day, the S.G.A. infants excreted significantly less hydroxyproline on the 3rd day of life in comparison with the preterm and normal term infants.

In a second study Younoszai et al. (1969) established that urinary peptidebound hydroxyproline on the first day of life averaged about 78% of the total hydroxyproline excretion in normal term infants and about 65% in premature infants, like the values of Morrow et al. (1966, 1967). The mean total hydroxyproline/creatinine ratio of term S.G.A. infants was slightly lower than that of normal term infants on the first day of life, whereas the ratio was relatively high in preterm infants. On the 10th day of life the ratio of the term S.G.A. had increased (like that of the normal term and preterm infants), but was now clearly

Table 2-3 Urinary hydroxyproline excretion in normal term, term S.G.A., and preterm newborns during the first 10 days of life

Authors	parameter studied	normal term newborns			term S.G.A. newborns			preterm newborns		
		day 1	day 3	day 10	day 1	day 3	day 10	day 1	day 3	day 10
Younoszai and Haworth (1968) (± s.d.)	total urinary hydroxyproline excretion mg/24 hr.	4.4 ± 1.0	9.9 ± 0.8	N.A.	3.5 ± 0.7	7.0 ± 0.6	N.A.	5.5 ± 0.5	9.6 ± 0.9	N.A.
Younoszai et al. (1969)	total hydroxyproline (mmol/l)/creatinine (mmol/l) ratio (± s.d.)	0.16	0.28	0.55	0.11	0.26	0.45	0.37	0.37	0.51
Klujber et al. (1972)	total urinary hydroxyproline excretion mg/24 hr. (± s.d.)	N.A.	13.3 ± 1.2	16.0 ± 2.2	N.A.	15.5 ± 1.6	23.7 ± 1.8	N.A.	9.4. ± 0.7	11.0 ± 0.8
	total hydroxyproline (μmol/l)/creatinine (μmol/l) ratio (± s.d.)	N.A.	0.27 ± 0.03	0.36 ± 0.05	N.A.	0.46 ± 0.06	0.76 ± 0.06	N.A.	0.43 ± 0.04	0.49 ± 0.03

N.A. = not available

lower than that of the other groups of infants. The values on the first day of life reflect what might be expected for their growth patterns during the latter days or weeks of pregnancy. S.G.A. infants grow little during this period, whereas premature infants are growing rapidly. However, the total hydroxyproline/creatinine ratio during the first week of life did not agree very well with the pattern of growth expected during this period of life when S.G.A. infants grow in general more rapidly than normal term or preterm infants.

Klujber et al. (1972) also investigated the mentioned 3 groups of infants and found that, except in the preterm infants (gestational age < 35 weeks and weighing less than 2,200 g), the daily urinary excretion of total hydroxyproline in normal 'term' (≥ 35 weeks and > 2,200 g) and 'term' S.G.A. (≥ 35 weeks and < 2,200 g) infants was considerably higher on the 3rd postnatal day than that reported by Younoszai et al. (1968). Their results show that on the 3rd day of life S.G.A. infants demonstrated the highest hydroxyproline excretion, suggesting a rapidly increasing turnover rate of collagen in S.G.A. infants associated with growth soon after birth. This rapidly increasing phase of growth activity was also strikingly shown by urinary excretion levels obtained on the 10th postnatal day: while no significant increase occurred from the 3rd to 10th day in normally grown term and premature infants, the S.G.A. group showed a highly significant rise in total hydroxyproline excretion whatever reference standard was used for comparison.

In view of these confusing findings Wharton et al. (1971) and Bissenden et al. (1978, 1979) determined the total hydroxyproline concentration in amniotic fluid at various stages of pregnancy. In their first study (Wharton et al., 1971) they showed that in normal pregnancy amniotic fluid total hydroxyproline concentration rose to a peak around the 28th week, before falling steadily

to term while creatinine concentration was at first constant and then rose rapidly to maximum values at term. The total hydroxyproline/creatinine ratio reached a zenith around 17 weeks and then fell rapidly. Total hydroxyproline concentrations tended to be lower in those pregnancies producing S.G.A. infants (birthweight < 10th percentile for gestational age) and those at particular risk of I.U.G.R. As changes in amniotic fluid total hydroxyproline and total hydroxyproline/creatinine ratio seemed to be related to intrauterine growth Bissenden et al. (1978 and 1979) also studied if fractionation of total hydroxyproline into its free and peptide components would increase the discrimination of the test. This turned out not to provide more information as there continued to be a considerable overlap with results from normal pregnancies.

Considering the above mentioned relation between anthropometric values (the ponderal index) and skeletal maturity at birth and the unique place of hydroxyproline in collagen turnover which mainly takes place in bone, the possibility to use hydroxyproline as a biochemical parameter for (prenatal) diagnosis of intrauterine malnutrition was considered. An investigation of the amount of total hydroxyproline excretion in the first urine of normally grown term infants and term infants malnourished in utero was started as amniotic fluid was not readily available for research purposes and as fetal urine makes a substantial contribution to the composition of amniotic fluid in late pregnancy when the fetal skin has become keratinised. The first urine is more or less comparable with amniotic fluid (Lind et al., 1972; Houston and Zeis, 1976) and may reflect the nutritional state of the fetus in utero with the advantage of the possibility to correlate this with anthropometric values at birth. Earlier studies in this field (Younoszai et al., 1968 and 1969; Klujber et al., 1972) resulted in conflicting results which may have been due to the

lack of quantification of the nutritional status of the examined newborns at birth. Therefore in our study the relation between the ponderal index and the urinary excretion of hydroxyproline after birth was investigated.

Normal term infants and infants affected by intrauterine growth retardation excrete constantly 70-80% of their total urinary hydroxyproline as peptidebound hydroxyproline during the first week of life (Klein and Teree, 1966; Morrow et al., 1966; Morrow et al., 1967; Younoszai et al., 1969). So total hydroxyproline excretion can be used as a measure of collagen turnover in the term infant. Allison et al. (1966) showed that as a measure of growth in postnatal life the ratio of hydroxyproline to creatinine in a 24-hour collection was an improvement on the absolute excretion of hydroxyproline, since the ratio partially corrects for body size and for differences in renal function. The hydroxyproline/creatinine ratio in 24-hour urine collections correlated well with random urine samples obtained during the same 24-hour period in the studies of Howells et al. (1967) and Younoszai et al. (1969), thus making 24-hour urine collections in our study unnecessary.

In our study (publication I) no correlation between the degree of intrauterine malnutrition and the total urinary hydroxyproline /creatinine ratio could be established, indicating that hydroxyproline excretion in the first urine of newborns cannot be used clinically as a measure of intrauterine malnutrition. Indirectly the conclusion of Bissenden et al. (1978 and 1979) was confirmed: the normal range of urinary hydroxyproline excretion being already wide, growth retardation in utero does not add a measurable and significant decrease to the hydroxyproline excretion in the first urine.

2.2 The ponderal index as an additional and refined measure to predict the neonatal morbidity of infants malnourished in utero

The perinatal mortality rate of neonates born before the 33rd week of gestation is relatively high. It decreases with advancing gestation and newborns with a gestational age of 38-39 weeks show the lowest mortality (Lubchenco, 1981). However, it becomes again progressively higher as gestation further advances (Gruenwald, 1964 a). The perinatal mortality rate of S.G.A. infants is substantially higher than the perinatal mortality rate of newborns whose birthweight is appropriate-for-gestational age (table 2-4). This is due to an increased incidence of both stillbirths and deaths occurring in the first week of life (Papaevangelou et al., 1972).

Table 2-4 Perinatal mortality (P.N.M.) rates of S.G.A. and A.G.A. infants versus overall figures*

Author(s), year of publication, are	Perinatal mortality rate			Remarks (definition of S.G.A.)
	S.G.A. infants	A.G.A. infants	All infants	
Usher, 1970, Canada	128.5 °/oo	14.3 °/oo	16.6 °/oo	birthweight > 1,000 grams S.G.A. = weight < P 3
Papaevangelou et al., 1972, Greece	374.2 °/oo	43.3 °/oo	55.8 °/oo	S.G.A. = weight < P 3 P.N.M. term S.G.A. infants: 113.9 °/oo P.N.M. term A.G.A. infants: 10.7 °/oo P.N.M. preterm S.G.A. infants: 704.2 °/oo P.N.M. preterm A.G.A. infants: 201.4 °/oo
Usher and McLean, 1974, Canada	189.3 °/oo	15.9 °/oo	20.6 °/oo	S.G.A. = weight < P 3
Huisjes, 1981, The Netherlands	79.3 °/oo	15.4 °/oo	24.2 °/oo	S.G.A. = weight < p 10

*The presented figures concern in general infants born after a gestation of 28 or more weeks

Neonatal mortality rates follow the same pattern as perinatal mortality rates: the neonatal mortality rate of term S.G.A. infants is higher than the neonatal mortality rate of infants whose birthweight is appropriate-for-gestational age as is illustrated in table 2-5.

Table 2-5 Neonatal mortality (N.M.) rates of term S.G.A. infants versus term A.G.A. infants

Author(s), year of publication, area	Neonatal mortality		Remarks (definition) of S.G.A.
	term S.G.A. infants	term A.G.A. infants	
Lugo and Cassady, 1971, USA	53.8 °/oo	12.6 °/oo	birthweight > 1,000 grams S.G.A. = weight < P 3
Papaevangelou et al., 1972, Greece	78.9 °/oo	5.4 °/oo	S.G.A. = weight < P 10
Lubchenco et al., 1972, USA	20.5 °/oo	5.0 °/oo	S.G.A. = weight < P 10 birthweight > 1,000 grams
Tejani and Mann, 1977, USA	16.1 °/oo	8.9 °/oo	S.G.A. = weight < P 5

Neonatal morbidity of a significant nature follows the same pattern as mortality (Lubchenco, 1981) which is not amazing as neonatal morbidity of S.G.A. infants is often the result of fetal disease and/or an insufficient supply line to the fetus in utero (Usher, 1970; Gruenwald, 1974). Tables 2-6, 2-7 and 2-8 present figures about the incidence of the most common clinical problems as a consequence of an insufficient supply line and table 2-9 indicates the incidence of some fetal diseases (congenital infections, congenital malformations and chromosomal anomalies) in S.G.A. infants. Though perinatal morbidity is the worthy successor of perinatal mortality as a yardstick of reproductive adequacy (Huisjes, 1981), reliable figures on neonatal morbidity of S.G.A. infants in the Netherlands are not readily available and tables 2-6 till 2-9 have been composed of many different studies in this field.

Table 2-6 Clinical problems of the S.G.A. infant: I Asphyxia, acidosis and hypothermia

Problem	Author(s), year of publication, area	S.G.A. infants	Normal newborns	Remarks (definition of S.G.A.*; definition of the problem)
Asphyxia	Beargie et al., 1970, USA	20%	?	term infants, S.G.A. = weight < P 10; asphyxia = positive pressure resuscitation at birth
	Lugo and Cassady, 1971, USA	27%	13%	S.G.A. = weight < P 10; asphyxia = Apgar score < 6 at 1 or 5 min.
	Papaevangelou et al., 1972, Greece	3.7%	0.8%	S.G.A. = weight < P 3; asphyxia = Apgar socre < 3
	MacDonald et al., 1980, USA	4.1%	0.36%	gestational age > 36 wks S.G.A. = weight < P 3; asphyxia = > 1 minute of positive pressure ventilation necessary
	Huisjes, 1981, The Netherlands	15.5%	9.7%	term infants, S.G.A. = weight < P 10; asphyxia = Apgar score < 6 at 1 min.
Acidosis	Jurgens-van der Zee, et al., 1979, The Netherlands	19.0%	9.0%	term infants, S.G.A. = weight < P 10; acidosis = umbilical vein pH < 7.20
Hypothermia	Low et al., 1978, Canada	28%	4%	gestational age > 34 wks, S.G.A. = weight < P 10; hypothermia = temperature < 36°C
	Ounsted et al., 1981, Gr. Britain	6%	?	S.G.A. = weight < P 3; hypothermia = not defined

*If gestational age is not mentioned, the presented figure(s) concern in general infants born after a gestation of 28 or more weeks

Table 2-7 Clinical problems of the S.G.A. infant: II Hypoglycemia

Problem	Author(s), year of publication, are	S.G.A. infants	Normal newborns	Remarks (definition of S.G.A.*; definition of the problem)
Hypoglycemia**	Lugo and Cassady, 1971, USA	12%	2%	S.G.A. = weight < P 10; def. = (2)
	Lubchenco and Bard, 1971, USA	25%	10%	term S.G.A. and A.G.A. infants, S.G.A. = weight < P 10; def. = (1)
		67%	15%	preterm S.G.A. and A.G.A. infants, S.G.A. = weight < P 10; def. = (1)
	de Leeuw and de Vries, 1976, The Netherlands	24%	?	majority born at term, S.G.A. = weight < P 10; def. = (1)
	Járai et al., 1977, Hungary	18%	?	S.G.A. = weight < P 10; def. = (2) (preterm S.G.A. 8.1% term S.G.A. 23.2% postterm S.G.A. 19.0%)
	Tejani and Mann, 1977, USA	7.5%	?	S.G.A. = weight < P 5; def. = (3) policy of early feeding
	Low et al., 1978, Canada	15%	7%	gestational age > 34 wks S.G.A. = weight < P 10; def. = (2)

* If gestational age is not mentioned, the presented figure(s) concern in general infants born after a gestation of 28 or more weeks.

**Definitions: (1) bloodglucose < 1.1 mmol/l
(2) bloodglucose < 1.1 mmol/l in preterm and < 1.6 mmol/l in term infants
(3) no definition stated

Table 2-8 Clinical problems of the S.G.A. infant: III Polycythemia/hyperviscosity, hyperbilirubinemia and transient respiratory distress

Problem	Author(s), year of publication, area	S.G.A. infants	Normal newborns	Remarks (definition of S.G.A.*; definition of the problem)
Polycythemia/ hyperviscosity**	Lugo and Cassady, 1971, USA	12%	2%	S.G.A. = weight < P 10; def. = (1)
	Wirth et al., 1979, USA	15-17%	4-5%	esp. prevalent among term and postterm infants, S.G.A. = weight < P 10; def. = (2)
	Hakanson and Oh, 1980, USA	17.7%	-	S.G.A. = weight < P 10; def. = (3)
	Stevens and Wirth, 1980, USA	-	4%	term A.G.A infants; def. = (4)
Hyperbilirubinemia***	Low et al., 1978, Canada	4%	2%	gestational age > 34 wks S.G.A. = weight < P 10
Transient respiratory distress****	Low et al., 1978, Canada	6%	2%	gestational age > 34 wks S.G.A. = weight < P 10

*If gestational age is not mentioned, the presented figure(s) concern in general infants born after a gestation of 28 or more weeks.

**Definitions used:

(1) capillary haematocrit > 70%

(2) capillary haematocrit > 70%, viscosity > 2 s.d. above the mean (Gross et al., 1973)

(3) viscosity > 2 s.d. above the mean (Gross et al., 1973)

(4) capillary haematocrit > 65%, viscosity according to Gross et al., 1973

***Defined as: requiring phototherapy or an exchange transfusion

****Defined as: indrawing, grunt, retraction, tachypna increased surveillance or oxygen therapy

Table 2-9 Congenital infections, congenital anomalies and chromosomal abnormalities* in S.G.A. infants and in the general newborn populations

Problem	Author(s), year of publication, area	S.G.A. infants	Overall figure	Remarks (definition of S.G.A.)
Congenital malformations and chromosomal anomalies	Colman and Rienzo, 1961, USA	5.4%	1.5%	S.G.A. = term infants, weight < 2500 g
	Scott and Usher, 1966, Canada	22.1%	3%	S.G.A. = weight < P 10
	Lugo and Cassady, 1971, USA	7%	2%	S.G.A. = weight < P 10
	Papaevangelou et al., 1972, Greece	8.1%	3.7%	gestational age > 34 wks S.G.A. = weight < P 3
	Lubchenco, 1976, USA	11.1%	3.3%	S.G.A. = weight < P 10; term S.G.A. : 9.2% congenital anomalies
	Treffers et al., 1981, The Netherlands	? ?	3.3% 0.21%	congenital anomalies chromosomal anomalies
Congenital infections	Beargie et al., 1970, USA	2.2%	?	S.G.A. = term infants, weight < P 10
	Alford, 1971, USA	?	0.5%	use of cord IgM

*As the figures of congenital anomalies and chromosomal abnormalities are difficult to separate in the different reports, they are presented together.

Normal labour may severely compromise the S.G.A. infant (Lin et al., 1980) when intrauterine hypoxia (Usher, 1970) due to an insufficient supply is present. Table 2-6 shows that neonatal asphyxia and acidosis tend to be more common in the S.G.A. infant. During the asphyxial insult the S.G.A. infant frequently passes meconium in utero (Fujikura and Klionsky, 1975) and develops a gasping fetal breathing pattern (Dawes, 1974) resulting in the aspiration of meconium with resulting aspiration pneumonia which may be complicated by pneumothorax and pulmonary haemorrhage (Bacsick, 1977). The overall incidence of meconium aspiration syndrome in live-born infants amounts to 1-3% (Brown and Gleicher, 1981), but the exact incidence in S.G.A. infants is not well known.

The relatively large surface area with decreased insulation

due to markedly diminished subcutaneous fat tissue may result in excessive heat loss with hypothermia in the S.G.A. infant (Sinclair, 1970), table 2-6.

The high frequency of hypoglycemia in S.G.A. infants (table 2-7) has been attributed to a deficiency of depot fat (Usher and McLean, 1974; Widdowson, 1974 a and b; Roord and Ramaekers, 1978), a deficient gluconeogenesis (Haymond et al., 1974; Kollée et al., 1979; Kollée et al., 1980) and a diminished glycogen storage at birth (Wigglesworth, 1967; Hill, 1974).

Hyperviscosity due to polycythemia is clearly an exaggerated response of the S.G.A. infant to intrauterine hypoxia with resultant erythropoietin production (Finne, 1966). Hypoxia, acidosis, hypothermia, and hypoglycemia may lead to decreased deformability of red blood cell membranes (Bergqvist, 1974) and increase the blood viscosity in addition. The incidence of hyperviscosity in healthy term A.G.A. infants (about 4%, see table 2-8) is considerable. This led recently to a discussion (Van der Elst et al., 1980) about the need to perform (partial) exchange transfusions (Kontras, 1972; Mentzer, 1978) in all these cases. In the presence of clinical symptoms most authors tend to take measures to reduce blood viscosity in order to prevent inadequate tissue perfusion and sludging.

Intrauterine growth retardation does not affect the physiologic maturation of fetal organs which develops according to gestational age. The incidence of hyperbilirubinemia and the respiratory distress syndrome in the term S.G.A. infant is only slightly above normal (table 2-8): hyperbilirubinemia occurs more often in cases of hyperviscosity and (transient) respiratory distress in cases of asphyxia. The susceptibility to infection of the S.G.A. infant in the neonatal period is increased (Papaevangelou et al., 1972), probably as a result of defective humoral (Papadatos et al., 1969; Chandra and Matsumura, 1979) and

cellular immunity (Ferguson, 1978).

Congenital infections, chromosomal and congenital anomalies are especially encountered in S.G.A. infants (table 2-9). The birthweight of siblings is of clinical significance: 80% of infants with rubella-embryopathy have a birthweight below the range of variability of birthweight within the sibship, but only 41-46% of them would have been considered small-for-gestational age using empirical charts (Turner, 1971). Except this comparative method of considering birthweight (in the multigravida) to assess retardation of intrauterine growth, clinically silent intrauterine infections can be established by estimating cord IgM levels (Alford et al., 1967; Tympner, 1971; Haider, 1972) though Matthews and O'Herlihy (1978) recently remarked that determination of cord IgM in S.G.A. infants did not help significantly in diagnosis of infections.

Not all S.G.A. infants will present signs of above mentioned morbidity patterns in the early neonatal period and the incidence of morbidity will also depend on the duration of the gestational age and the maturity of the infant. About 35% of the S.G.A. infants escape all problems at delivery and in the neonatal period (Ounsted et al., 1981), resume growth soon after birth, and can be discharged early. The majority suffers from one or more of the above mentioned (causative interrelated) complications which may lead to longterm morbidity. To facilitate the recognition of those term S.G.A. infants who are at high risk of neonatal complications, we turned to the ponderal index as a measure to quantify intrauterine malnutrition. In two studies we tried to establish if the ponderal index might be helpful at birth to select those growth retarded infants at high risk. The first one (publication II) reports on the nutritional status (quantified by birthweight for gestational age and by the ponderal index) and the neonatal morbidity of a group of 500 term

newborns. The second paper (publication III) presents the morbidity pattern of 46 severely S.G.A. term infants (birthweight < P 2.3 for gestational age) according to their nutritional status (using again the ponderal index). Both publications point to the fact that especially disproportionally grown term (S.G.A.) infants are at high risk of neonatal complications in comparison with proportionally grown term S.G.A. infants. The ponderal index turned out to be a useful measure to predict neonatal morbidity (in addition to the usual classification according to birthweight for gestational age).

Publication II demonstrates that nearly 40% of the term S.G.A. infants (infants whose birthweight is below the 10th percentile for gestational age on the Kloosterman curves) were clearly disproportionally grown as they had a P.I. below the 10th percentile of Miller and Hassanein (1971). But of the infants whose birthweight was above the 10th percentile for gestational age 8.1% also had a ponderal index below the 10th percentile and were disproportionally grown. Term infants with a birthweight and a P.I. below the 10th percentiles showed more often neonatal problems (like asphyxia, acidosis, hyperviscosity, hypoglycemia, and hypothermia) than proportionally grown term S.G.A. infants. Disproportionally grown term infants with a birthweight above the 10th percentile also had a greater morbidity than proportionally grown term infants with a birthweight above the 10th percentile, though their morbidity remained below that of disproportionally grown term S.G.A. infants.

Of the 46 term, severely S.G.A. infants (birthweight < P 2.3 for gestational age on the Kloosterman curves) in publication III 23 (50%) were disproportionally grown (P.I. < P 3 according to Miller and Hassanein, 1971), indicating that the percentage of disproportionally grown infants increases when birthweight for gestational age falls off. Whereas in publication II 52% of

S.G.A. infants with a birthweight < 10th percentile escaped without neonatal morbidity, this percentage was lower among the S.G.A. infants with a birthweight < 2.3 percentile in publication III. In the series of Ounsted et al. (1981) only 35% of the S.G.A. infants (birthweight < 3rd percentile) escaped any perinatal problems, but that study was performed over a long period (1964 - 1977) during which perinatal care progressed quickly.

As there occurs a higher incidence of neonatal morbidity in severely S.G.A. infants than in moderately S.G.A. infants, the incidence of neonatal morbidity increases when the ponderal index decreases (and disproportional growth prevails). So both underweight-for-gestational age and underweight-for-length (small ponderal index, disproportional growth) predispose term infants to neonatal morbidity.

2.3 Postnatal growth of newborns affected by intrauterine malnutrition

At birth the size of a term infant correlates more with the size of the mother than with the size of the father (Tanner et al., 1956) and term male newborns are in general longer, heavier, and have a greater head circumference than female newborns (Usher and McLean, 1969; Kloosterman, 1970). The faster late fetal growth of the male fetus can be explained by testosterone production from the testicles after 32 weeks of gestation (Smith, 1977). This accelerated growth of the male as compared to that of the female continues for 3 to 6 months after birth (Smith, 1977). Thereafter the serum testosterone levels are low in both sexes and there is no appreciable sex difference in growth rate until the advent of adolescence. Given an adequate environment, the infants shift after birth from a growth rate that is predominantly determined by maternal factors to one that is increasingly related to its own genetic background, as exemplified by the mid-parental height

(Smith et al., 1976). For about two thirds of normal infants, the linear growth rate shifts during the first 12 to 18 months of life. The number shifting upward and the number shifting downward in growth rate are about equal (Smith et al., 1976). Infants who are relatively small at birth but whose genetic background indicates larger size begin their acceleration toward the new growth rate soon after birth, and they have achieved a new channel of growth by 4 to 18 months of age (Smith et al., 1976). Those who are relatively large at birth but whose genetic background is for smaller size tend to maintain the prenatal growth rate for several months before beginning their deceleration into a lower growth channel, which is usually achieved by 8 to 19 months of age (Smith et al., 1976). Though at birth first-born term newborns are smaller than average, by 1 year of age they have usually shifted in growth rate and are slightly longer than subsequent offsprings (Smith, 1977).

Whereas in infancy major shifts in growth rate occur, by the age of 18 months to 2 years the child enters an era of stable growth. Already toward the latter part of the first year, there is a gradual diminution in growth rate and from 2 years onwards the child grows fairly consistently at a rate of 5 to 7.5 cm yearly. Adolescence is the period of gonadotrophin-induced maturation and linear growth acceleration. Most linear growth has been achieved by the age of 18 years, with an average of 1 cm in further growth taking place between 18 and 21 years (Roche and Davila, 1972).

Some of the numerous factors affecting the rate of postnatal growth and the ultimate size of a child have been mentioned already. However, numerous factors are known to play a role: genetic factors (the mid-parental height), genetic sex differences (due to the presence of the Y chromosome), genetic racial differences (Asiatic children tend to be smaller than either the

black or the white child; Barr et al., 1972), social class or socio-economic status, parity, season (in England children grow faster in the summer than in the winter; Marshall, 1971), nutrition (inadequate intake, malabsorption), environment (neglect, abuse), endocrine factors (testosterone, estrogens, pituitary growth hormone and somatomedin, thyroid hormone), chronic diseases (such as cardiac defects, renal dysfunction, chronic serious infectious disease, metabolic disorders), and mental deficiency (Doorn, 1967).

The somatic postnatal growth of S.G.A. newborns will depend on the etiology of the intrauterine growth retardation, the extent of associated perinatal insults, and the above mentioned numerous factors. Infants with decreased growth potential such as those with chromosomal disorders (like the Turner syndrome), with fetal intoxications (like the fetal alcohol syndrome), with congenital malformations (like chondrodysplasia), or with congenital infections (like rubella), can be expected to grow less well after birth as the small size at birth is often due to a deficient number of cells. But in the majority of S.G.A. infants no cause can be identified which explains their growth retardation in utero (see 1.3).

When one surveys the literature dealing with the postnatal growth of S.G.A. infants, one finds a surprising dearth of good studies. Many early papers are invalidated by the lack of adequate assessment of gestational age leading to the failure to distinguish S.G.A. infants from premature A.G.A. infants (Dubowitz, 1974). Therefore only studies performed since the early seventies are worthwhile to review.

One of the best studies has been that of Fitzhardinge and Steven (1972 a). They did a follow-up study of 96 S.G.A. singleton nfants born in Montreal (Canada) in the years 1960-1966. The

infants in the study had a gestational age of greater than 38 weeks, a birthweight at more than 2 standard deviations below the expected weight for gestational age (equivalent to a weight below the 3rd percentile), and no obvious cause for the underweight in the way of congenital malformations, infections, chromosomal disorders and so on. Disproportionate and proportionate I.U.G.R. were not distinguished: though all the infants were more than 2 standard deviations below the expected weight at birth, 67% were more than 2 s.d. below the expected length and 76% below the expected head circumference. At the age of 6 months the average weight and length for the group were between the 10th and 25th percentile, but at six years 35% were still below the 3rd percentile in weight and height and only 8% above the 50th percentile. A comparison at follow-up of the 45 infants whose length at birth was below the 3rd percentile with the rest of the group (above the 3rd percentile at birth) showed no significant difference between the two, with both groups being below the 50th percentile. Assessment of growth velocity by 6-monthly increments showed that those S.G.A. infants whose height eventually exceeded the 3rd percentile had a greater velocity in the first 6 months after birth than the remaining infants, but no difference in velocity after 6 months. Correlation of the growth retardation at follow-up with various maternal and environmental factors showed a positive correlation with socio-economic status only.

The general picture which emerges from the study of Fitzhardinge and Steven (1972 a) and other studies about the postnatal growth of term S.G.A. infants (Babson, 1970; Cruise, 1973; Dubowitz, 1974; Smolders-de Haas, 1974; Martell et al., 1978; Davies et al., 1979) is that the rates of weight gain, length and head circumference growth of S.G.A. infants are higher than in those of A.G.A. infants during the first 6 months after birth. Thereafter (none of these studies provides information about

growth after the age of 6 years) the differences in growth rates between S.G.A. and A.G.A. infants are not significant anymore. This accelerated growth is called 'catch-up' (but it does not refer to the ultimate size attained). Studies about the postnatal growth of S.G.A. infants whose gestational age is not stated (Ounsted and Taylor, 1971; Ounsted and Ounsted, 1973; Chamberlain and Davey, 1975; Chamberlain and Simpson, 1977) and which probably describe a mixture of preterm and term S.G.A. infants, confirm the described general picture. An interesting feature is that head circumference reaches its maximum rate of growth earlier than weight and length (Fujimura and Seryu, 1977; Davies et al., 1979). As head circumference is closely related with brain weight (Cooke et al., 1977), the recovery of intrauterine growth retardation of the brain seems more important for the S.G.A. infant than the recovery of his weight and length growth deficit. Another interesting fact is that in animals whose maturity at birth is comparable with humans (like guinea pigs), the rate of postnatal growth is also related to the size at birth (Widdowson, 1974 b). If rats are starved during the 'brain growth spurt' (see 2.4), a critical period of development during the first weeks of life, the subsequent rate of growth is diminished despite the availability of a liberal supply of food and at maturity these animals have a relatively small size (Widdowson and McCance, 1963; Winick and Noble, 1966).

Davies et al. (1979) studied the somatic growth in the first 3 months after birth of disproportionally growth term S.G.A. newborns (with a ponderal index below the 3rd percentile) and showed that these newborns gain more rapidly in weight, length and head circumference than more proportionally grown term S.G.A. infants (with a ponderal index between the 10th and 50th percentile). In both groups rates of growth in each of the 3 months after birth were greater than in term A.G.A. infants. Furthermore Davies and

Beverly (1979) demonstrated that on average S.G.A. infants increase their weight relatively more than their length, so that by the end of the first year they have similar body proportions as A.G.A. infants. Whereas at birth the average ponderal index of this group of S.G.A. infants was relatively low in comparison with A.G.A. infants, at 12 months of age the difference was not significant anymore. However, disproportionally grown term S.G.A. infants continue to be shorter and lighter than A.G.A. infants at 1 year of age (Davies and Beverly, 1979). Chamberlain et al. (1975 and 1977) remarked that S.G.A. infants were often relatively underweight-for-length at 22 and 42 months of age, but they did not quantify this using a weight-length ratio like e.g. the ponderal index and did not provide information about disproportionate and proportionate I.U.G.R. at birth among the S.G.A. infants followed-up in their study.

Gruenwald (1974) supposed that I.U.G.R. in the later weeks of pregnancy (i.e. disproportionate I.U.G.R.) would result in complete catch-up growth after birth. The available literature dealing with this subject is scarce and provides only useful information about the postnatal growth of disproportionally grown S.G.A. infants during the first year of life (Davies, 1980 and 1981). But it indicates that the hypothesis of Gruenwald may not be valid. To investigate the ultimate outcome of this subgroup of S.G.A. infants we followed-up a group of disproportionally grown term infants till the age of 3 years, when they will have reached their definite channel of growth (Smith et al., 1976). Strict selection criteria were applied to avoid confounders influencing postnatal growth. Only term born Caucasian singletons free from additional perinatal complications (like artificial delivery, asphyxia, acidosis, hypoglycemia, hyperviscosity, hyperbilirubinemia, hypothermia, and respiratory difficulties) and from fetal

diseases (congenital malformations, infections, chromosomal anomalies) were selected. Disproportionate I.U.G.R. was defined by a birthweight below the 10th percentile for gestational age (Kloosterman, 1970) and a ponderal index (100 x W/L^3) below the 10th percentile for gestational age of Lubchencc et al. (1966). The 10th percentile of the ponderal index curves of Lubchenco et al. (1966) corresponds to the 5th percentile for gestational age of the ponderal index curves of Miller and Hassanein (1971).

At 3 years of age (mean age 38 $\pm$ 3 months) we reviewed their somatic growth in combination with a group of healthy controls matched for age, sex, birth rank, and social class. The average height of the parents of the two groups was comparable, excluding genetic variations. Weight, length, head circumference, skinfold, and skeletal maturity were used as parameters to establish if disproportionate intrauterine growth results in complete catch-up growth over the first 3 years of life. Skinfold measurements and the estimation of skeletal maturity have rarely been used during follow-up studies of S.G.A. infants, and were included in the examination proforma as these two measures proved to provide essential information about the nutritional status at birth (Roord et al., 1978).

Standard physical measurements were obtained shortly after birth by Roord and Ramaekers (1978). Weight was estimated with the newborn fully unclothed. The crown-heel distance was determined with the baby supine, with both legs extended and lying on a measuring scale with a fixed head-plate and a movable foot-plate (neonatometer). Miller and Hassanein (1971) found variations in crown-heel measurements not exceeding 2% (the influence on the ponderal index of a variation in length of $\pm$ 1% would be $\pm$ (1-0.9706) = $\pm$ 3% of the index). Head circumference was measured 24 hours after birth using a non-stretchable tape placed from the maximal occipital prominence around to the area just

above the eyerbows. Length was recorded until 18 months of age, whereafter height was obtained using a stadiometer. At follow-up weight was measured with the child largely unclothed and head circumference measurements were performed as in the neonatal period. These measurements were obtained as accurately as possible by several observers, all of whom had been carefully taught the technique of measurements and were unaware of the category. A high degree of accuracy and consistency could be achieved. At 3 years of age all physical measurements were performed by the writer using the same techniques and unaware of the category.

Publication IV shows that despite the presence of postnatal catch-up growth in the first 6 months after birth the term infants who were disproportionally growth retarded at birth continued to be underweight-for-length and lean (relatively small skinfold values) at the age of 3 years. The upward shift in length and head circumference was greater than for weight.

Publication V indicates that whereas at birth the infants malnourished in utero had a significant retardation in skeletal maturity, at 3 years of age their average skeletal maturity approached that of the healthy controls. However, those intrauterine malnourished children with a length below the national 10th percentile still showed at 3 years of age a retarded skeletal growth in comparison with those who had reached a length above the 10th percentile for age.

2.4 Developmental aspects of intrauterine malnutrition

In a recent large-scale follow-up study Neligan et al. (1976) demonstrated that both children who are 'born too soon' and those who are 'born too small' show some impairment of performance when they reach school-age, and that those 'born too small' are at a greater disadvantage and appear less likely to show normal development. Their results point to the fact that when a child is

'born too soon', but with an otherwise normal intrauterine growth pattern, he will continue to develop normally if he can be protected from the dangerous neonatal complications of premature birth, and can be kept in an adequate nutritional state to continue his normal pattern of growth. But, when a child's growth pattern has already been impaired in utero, his whole subsequent development may be significantly impaired in a manner which cannot be remedied by improvements in neonatal care. Except biological and clinical factors, environmental factors, and especially the quality of the mother's care of her child, are of great importance (Drillien, 1970; Neligan et al., 1976). Despite this latter feature the above mentioned conclusions hold out.

Gruenwald (1963) first called attention to the fact that whereas the liver, spleen, adrenals and thymus are severely reduced in size in S.G.A. infants, the brain appears to be the least affected. The human brain initiates the period of rapid weight gain during the last half of fetal life, with a peak near the time of birth which then decreases over the first year of postnatal life (Dobbing and Sands, 1979). There are two major periods of brain cell multiplication: one, the neuroblasts, from 15-20 weeks of gestation and one, the glia, which commences at about 25 weeks of gestation, this second period probably ends in the second year after birth (Dobbing and Sands, 1970). Approximately two-thirds of the human brain cells, as represented by DNA, accumulate prior to birth (Winick, 1968). The 'brain growth spurt' may be a period of enhanced vulnerability to nutritional restriction (Dobbing and Sands, 1979). Timing in relation to birth, severity and duration of intrauterine growth retardation will determine the final growth limitation of the brain. In guinea pigs (who like humans initiate the brain growth spurt in utero) adequate postnatal nutrition offsets some, though not all of the biochemical changes resulting from intrauterine growth

retardation: especially the quantity of DNA in the cerebellum remained reduced at reaching maturity (Chase et al., 1971). Thomas et al. (1979) demonstrated by means of stereological analysis of the brains of rats undernourished from birth (within the brain growth spurt) a deficit in the synapse to neuron ratio. The question arises if in human beings the brain changes produced by intrauterine growth retardation are functionally important and reversible during the period of nutritional rehabilitation after birth.

The combination of prematurity and S.G.A. might lead to higher incidence of handicap than one of these factors alone. Commey and Fitzhardinge (1979) established major neurological handicaps in 49% of a group of premature S.G.A. infants followed-up for two years after birth. Major neurological problems (like cerebral palsy and epilepsia) and hearing and vision disturbances are uncommon in S.G.A. infants born at term, but evidence of minimal brain dysfunction is present in 25% and speech deficits in about 30% (Fitzhardinge and Steven, 1972 b) at the age of 4-6 years. Though intelligence quotient scores do not differ appreciably from A.G.A. infants (Babson and Kangas, 1969; Fitzhardinge and Steven, 1972 b) about one-third of the S.G.A. infants are failing in school (Fitzhardinge and Steven, 1972 b; Parkinson et al., 1981) where behaviour problems are more often encountered than normally (Parkinson et al., 1981). From the studies of Fitzhardinge and Steven (1972 a and b) the remarkable feature emerged that in a group of term S.G.A. infants selected by birthweight only the severity of intrauterine growth retardation (related to weight deficit at birth) did not show a correlation with ultimate growth achievement and with subsequent developmental outcome. This observation induced the question if a short period of intrauterine growth retardation (recognizable at birth as disproportionate growth) might lead to an impaired postnatal

development.

To answer this question we thoroughly reviewed at the age of about 3 years a group of children who presented disproportionate I.U.G.R. at birth (synonyms: intrauterine malnutrition, subacute fetal distress). The children in the study group and the controls (see the selection criteria in 2.3) whose growth parameters have been discussed in publications IV and V were subjected to an assessment of their behaviour, neurological functioning, and language development according to age-appropriate proformata. Behaviour and language can be considered as complex cerebral functions which develop and extend quickly over the first years of life. Clinical experience suggests that cerebral dysfunction is often accompanied by behaviour problems and also by language delay. Dysfunction of the nervous system was substantiated by assessment of the neurological development. The values of behaviour and language development were considered as possible additional indicators of cerebral dysfunction. Except the fact that this subgroup of S.G.A. infants (disproportionate I.U.G.R.) had not yet been studied in this way, the children in our study benefited in contrast with the above mentioned studies fully of the introduction of intensive prenatal and postnatal care as well as of early and high-caloric nutrition (de Leeuw, 1972; Brandt, 1981).

Publication VI shows the results of the behaviour and neurological assessments and publication VII provides the language achievements in relation to the data presented in publication VI. Behaviour was studied using the behaviour screening questionnaire (B.S.Q.) of Richman and Graham (1971), the items of problem behaviour concerned: 1) eating, 2) sleeping, 3) soiling, 4) activity, 5) concentration, 6) relations with other children, 7) attention seeking and dependency, 8) difficulty to manage, 9) tempers, 10) mood, 11) worries and 12) fears. As parental reports

on specific items of behaviour might be inaccurate, a behaviour observation report (B.O.R.) was composed of all children. This consisted of 8 items: 1) activity, 2) concentration, 3) attention seeking and dependency, 4) negativism, 5) insistency, 6) destructivity and aggression, 7) fidgetiness and 8) fears.

Neurological dysfunction was studied using the 26 items suitable for children of 3 years of age of the examination proforma for minor neurological dysfunction of Touwen (1979).

The Reynell Developmental Language Scales (Reynell, 1969) were used to test language and the results were related to the assessment of behaviour and neurology.

Both problematic behaviour and neurological dysfunction occurred more frequently (in about one third of the children) in the group of disproportionally grown infants. Furthermore both verbal comprehension and expressive language were significantly less developed in infants malnourished in utero. A firm relation could be established between language delay and behaviour problems, a feature well known to speech therapists (Baker et al., 1980; Mattison et al., 1980). Language delay and neurological dysfunction were als interrelated and this applied also to neurological dysfunction and behaviour problems.

These studies point to the fact that disproportionate intrauterine growth retardation often results in signs of brain dysfunction at the age of 3 years and that behaviour problems, neurological dysfunction and language delay are comparable as indicators of brain dysfunction at that age. Disproportionally grown newborns turned out to be a group at high risk for development delay.

Summary

Already in the early sixties it was emphasized that not all low birthweight infants (less than 2,500 gram) were born prior to term. Ensuing studies showed that about one third of all infants of low birthweight are small-for-gestational age (S.G.A.) and have experienced intrauterine growth retardation. Whereas the follow-up studies of low birthweight infants born during the 1950's and early 1960's demonstrated a significant incidence of handicaps, the results of subsequent studies with improved perinatal care indicated an increasing number of surviving children. It is now recognized that a substantial number of the infants of these early studies were of low birthweight because of growth retardation rather than preterm birth and that the prognosis of small-for-gestational age infants is different from the prognosis of preterm infants.

At present intrauterine growth retardation is generally defined as a birthweight below the 3rd, 5th or 10th percentile for a given gestational age. However, this definition characterizes a variety of conditions which all ultimately affect fetal growth. The etiological classification of fetal deprivation distinguishes adverse conditions 'intrinsic' to the fetus and/or placenta (like chromosomal anomalies) and 'extrinsic' factors acting on the fetus and/or placenta (like intrauterine infections and hypertension/toxemia). Clinically, growth retarded newborns can be divided into those with obvious fetal diseases (chromosomal anomalies, congenital malformations and infections) and those without. Daily practice has shown that in the vast majority of S.G.A. infants no obvious cause can be identified which may explain their retarded growth.

If genetically small infants are left out of consideration the growth retarded newborns without fetal diseases can be subdivided

according to the timing and duration of the intrauterine growth retardation. When the growth retardation started early in the third trimester (and has a duration of months) the infant will be proportionally small with respect to weight, length and head circumference (proportionate intrauterine growth retardation, or chronic fetal distress according to Gruenwald).

A second type of intrauterine growth retardation (disproportionate intrauterine growth retardation, or subacute fetal distress according to Gruenwald) reflects disproportionate growth: weight is more affectd than length and head circumference as the factors modifying fetal growth are operative only in the last weeks of pregnancy and the weight-length ratio will be reduced. Disproportionate intrauterine growth retardation (or 'intrauterine malnutrition' as these infants appear 'wasted' at birth) and proportionate intrauterine growth retardation can be separated objectively by quantifying the degree of disproportion using a weight-length ratio like the ponderal index ($100 \times W/L^3$).
In the presented papers the ponderal index was used at birth to quantify the nutritional status of term infants affected by intrauterine malnutrition.

In 2.1 and publication I the possibility is considered to use the urinary total hydroxyproline excretion as a biochemical parameter for the diagnosis of 'intrauterine malnutrition. This seemed conceivable as urinary hydroxyproline excretion is known to reflect the growth rate in early infancy and in young children, as hydroxyproline is a reliable index of bone collagen metabolism, and as skeletal growth is retarded in intrauterine malnutrition and correlates in a highly significant manner with the ponderal index. In this study the severity of the malnutrition was quantified by the deviation of the P.I. from 'normal'. By chemical analysis the total hydroxyproline excretion in the first urine sample passed after birth was determined as well as

the creatinine excretion. As creatinine excretion is correlated with body size and muscle mass, the total hydroxyproline (mmol/l) / creatinine (mmol/l) or THP/Cr. ratio was used instead of the absolute values of the total hydroxyproline excretion as it gives more consistent results for subjects of the same biological age. Single samples of urine could be used because these show a good correlation with 24-hour collections of urine. 50 Selected term infants whose nutritional status ranged from severe disproportional growth retardation to normal were investigated. No correlation between the degree of intrauterine malnutrition and the THP/Cr. ratio could be established, indicating that urinary hydroxyproline excretion cannot be used clinically as a measure of intrauterine malnutrition of the newborn, probably because near term intrauterine growth is retarded already under normal conditions. The normal range of urinary hydroxyproline excretion being already wide, intrauterine malnutrition does not add a measurable and significant decrease to the hydroxyproline excretion. As the first urine of newborns closely resembles amniotic fluid, the determination of hydroxyproline levels in amniotic fluid to quantify intrauterine malnutrition prenatally will probably not be very useful in clinical practice.

In 2.2 and publication II the incidence of 6 common neonatal complications (asphyxia, acidosis, hypothermia, hyperviscosity, hypoglycemia, and hyperbilirubinemia) was analysed in a group of 500 term infants subdivided by their distribution on the percentile blocks of birthweight for gestational age and of the ponderal index. The results showed that a small ponderal index predicts more accurately the occurrence of neonatal complications (except hyperbilirubinemia) than a low birthweight for gestational age (defined as weight below the 10th percentile). In the group of small-for-gestational age infants especially those infants showing disproportional growth retardation at birth

(diagnosed by a small ponderal index) suffer from neonatal complications. The latter feature was further investigated in a group of term very small-for-gestational age infants (birthweight below the 2.3 percentile for gestational age) in publication III. Again the disproportionally grown infants showed more neonatal complications than the more proportionally grown infants. From papers II and III the conclusion can be drawn that a small ponderal index (especially below the 10th percentile) selects those term (small-for-gestational age) infants at high risk of neonatal complications.

In 2.3 and publications IV and V the physical growth in early childhood of a group of 25 normal term A.G.A. infants is compared with a group of 25 term S.G.A. infants presenting clinical signs of intrauterine malnutrition and a small ponderal index at birth. Both groups were free from other perinatal morbidity and chronic diseases and were carefully matched for age, sex, birth rank and social class. Weight, length, head circumference, skinfold, and skeletal maturity have been studied as parameters of postnatal growth. Despite the presence of catch-up growth during the first 6 months after birth the infants malnourished in utero were still underweight-for-length with lower mean skinfold measures and a smaller mean head circumference at the age of 3 years in comparison with the matched controls. Though at birth the infants malnourished in utero had a significant retardation in skeletal maturity, at 3 years of age their average skeletal maturity approached that of the controls. However, those deprived infants with a length below the national 10th percentile at the age of 3 years still showed a retarded skeletal growth in comparison with those who had reached a length above the 10th percentile. So it can be said that infants presenting signs of intrauterine malnutrition at birth grow less well than normal controls (despite a period of catch-up growth) and behave in this respect like S.G.A.

infants in general. This may be due to the presence of many disproportionally grown infants in the groups of S.G.A. infants studied by other authors.

Section 2.4 and publications VI and VII describe the behaviour, the neurological development, and the language development of the same infants described in section 2.3 and publications IV and V at the age of 3 years. Behaviour was studied using the behaviour screening questionnaire (B.S.Q.) of Richman and Graham and a behaviour observation report (B.O.R.). The incidence of problematic behaviour among the infants malnourished in utero was high: hyperactivity and concentration disorders on one side and exaggerated fears on the other side were two characteristic patterns of behaviour. Neurological dysfunction and language delay occurred in about one third of the intrauterine malnourished infants. Language delay was often seen in growth reduced infants with significant behaviour problems, a problem well known to speech therapists. Neurological dysfunction and language delay as well as neurological dysfunction and behaviour problems turned out to be interrelated also. The results demonstrate that intrauterine malnutrition often results in signs of brain dysfunction at the age of 3 years and that behaviour problems, neurological dysfunction, and language delay are comparable as indicators for brain dysfunction at the age of 3 years. Early diagnosis of brain dysfunction by means of the described methods should be stressed in these infants.

Finally it is obvious that infants malnourished in utero (disproportionate growth retardation, subacute fetal distress) are at high risk of neonatal complications (like asphyxia, acidosis, hypoglycemia, hyperviscosity, and hypothermia), disturbed physical growth and brain dysfunction in early childhood. The calculation of the ponderal index at birth deserves a place beside the estimation of birthweight for gestational age as a

means to recognize these infants: a small value (e.g. below the 10th percentile for gestational age) should irrespective of the birthweight of the newborn be interpreted as a reason to consider the infant at an increased risk of neonatal and early childhood morbidity.

Samenvatting

In de jaren zestig werd in toenemende mate duidelijk dat niet alle pasgeborenen met een laag geboortegewicht (waarvoor veelal een grens van 2500 gram wordt gehanteerd) te vroeg (prematuur) geboren waren. Ongeveer één derde van alle pasgeborenen met een laag geboortegewicht bleek veel te licht van gewicht voor de opgegeven zwangerschapsduur (small-for-gestational age) en tijdens de zwangerschap (intrauterien) onvoldoende gegroeid te zijn. Een aanzienlijk percentage van de kinderen met een laag geboortegewicht die in de jaren vijftig en het begin van de jaren zestig geboren waren, bleek later meer of minder gehandicapt te zijn. Meer recente onderzoeken hebben laten zien dat een verbeterde perinatale zorg voor de zwangere moeder en haar pasgeboren kind leidt tot een betere prognose van kinderen met een laag geboortegewicht. Het ontbreken in bovenvermelde studies van een onderverdeling in prematuren en in pasgeborenen die intrauteriene groeivertraging doormaakten, heeft ertoe geleid dat deze onderzoeken geen goed antwoord kunnen geven op de vraag hoe de prognose van een kind met intrauteriene groeivertraging ingeschat moet worden en dit wordt actueel door de sterk toegenomen mogelijkheden van de perinatale medische zorg in het laatste decennium. Verder is ondertussen duidelijk geworden dat pasgeborenen met een laag geboortegewicht voor de zwangerschapsduur zeker geen homogene groep vormen.

Intrauteriene groeivertraging wordt in het algemeen gedefinieerd als een geboortegewicht beneden de 3e, 5e of 10e percentiel voor de zwangerschapsduur. Echter, aan de hand van deze definitie wordt een groep pasgeborenen geselecteerd waarvan de groeivertraging op verschillende grondslagen kan berusten. Bij de indeling naar de etiologie van de intrauteriene groeivertraging onderscheidt men 'ongunstige' factoren welke hun oorsprong vinden

in de foetus en/of de placenta (zoals chromosomale aandoeningen) en 'ongunstige' exogene factoren welke inwerken op de foetus en/of de placenta (zoals intrauteriene infecties en hypertensie /toxicose). Bij klinisch onderzoek kunnen pasgeborenen die intrauteriene groeivertraging doormaakten, worden onderscheiden in kinderen met en zonder duidelijke aangeboren ziekten (zoals chromosomale aandoeningen, aangeboren afwijkingen en infecties). De dagelijkse praktijk leert echter dat de genoemde factoren slechts in een klein percentage van de pasgeborenen met intrauteriene groeivertraging een rol spelen, veelal is er geen directe oorzaak aan te wijzen voor de groeivertraging in utero.

In gevallen van intrauteriene groeivertraging zonder dat er sprake is van een foetale ziekte of een genetisch klein kind kan men een onderverdeling aanbrengen aan de hand van de duur van groeivertraging. Als de groeivertraging vroeg in het derde trimester begint (en maandenlang duurt), zullen alle lichaamsmaten (gewicht, lengte en schedelomtrek) evenredig (geproportioneerd) klein zijn. Gruenwald spreekt in deze gevallen van chronische foetale distress, hetgeen hetzelfde is als geproportioneerde intrauteriene groeivertraging. Begint de groeivertraging pas in de laatste weken van de zwangerschap, dan zal het gewicht opvallend verlaagd zijn terwijl de lengte en de schedelomtrek nagenoeg normaal zijn. De pasgeborene zal er sterk 'vermagerd' (gedisproportioneerd) uitzien en de gewicht/lengte verhouding zal kleiner uitvallen. In deze gevallen wordt gesproken van subacute foetale distress (volgens Gruenwald) of beter: gedisproportioneerde intrauteriene groeivertraging. Gedisproportioneerde en geproportioneerde intrauteriene groeivertraging kunnen objectief worden onderscheiden door de mate van disproportionele groei te kwantificeren met behulp van een gewicht/lengte ratio zoals de ponderal index (100 x gewicht in grammen/lengte in centimeters tot de derde macht). In deze dissertatie werd steeds van genoemde ponde-

ral index gebruik gemaakt om bij de geboorte de voedingstoestand van de à terme pasgeborene te bepalen.

Sectie 2.1 en publicatie I behandelen de mogelijkheid om de uitscheiding van hydroxyproline in de urine te gebruiken als biochemische maatstaf voor de diagnostiek van intrauterine groeivertraging bij de pasgeborene. Voor deze mogelijkheid pleiten de observaties dat de uitscheiding van hydroxyproline in de urine goed correleert met de groeisnelheid van zuigelingen en jonge kinderen, dat hydroxyproline een betrouwbare index is van het collageenmetabolisme in het skelet en dat de skeletrijping vertraagd is bij gedisproportioneerde groeivertraging en goed correleert met de ponderal index. Bij dit onderzoek werd de ernst van de intrauteriene groeivertraging gekwantificeerd door middel van de deviatie van de ponderal index ten opzichte van de 50e percentiel. Door middel van chemische analyse werd de totale hydroxyproline en de creatinine uitscheiding bepaald in het eerste urinemonster dat na de geboorte werd geloosd. Omdat de creatinine uitscheiding correleert met de lichaamsgrootte en de spiermassa, werd de totale hydroxyproline (mmol/l) / creatinine (mmol/l) of THP/Cr. ratio gebruikt in plaats van de absolute waarden van de totale hydroxyproline uitscheiding. Deze ratio levert meer consistente resultaten op voor personen van eenzelfde biologische leeftijd. Kleine monsters urine konden worden gebruikt omdat deze goed correleren met volledige 24 uurs urine porties. 50 Geselecteerde à terme pasgeborenen werden onderzocht, hun voedingstoestand varieerde van sterk gedisproportioneerde groeivertraging tot normaal. Er kon geen relatie worden vastgesteld tussen de ernst van de groeivertraging en de THP/Cr. ratio. Dit houdt in dat de urine uitscheiding van hydroxyproline voor de kliniek geen bruikbare maat kan vormen om de ernst en/of duur van de doorgemaakte intrauteriene groeivertraging vast te stellen. Dit is waarschijnlijk het gevolg van het feit dat de intrauteriene groei

normaliter al afneemt bij het bereiken van de à terme datum. Aangezien de normale variatie in de hydroxyproline uitscheiding in de urine al groot is, verlaagt intrauteriene groeivertraging de uitscheiding ervan onvoldoende om meetbare verschillen op te leveren. De eerste urine van pasgeborenen lijkt sterk op vruchtwater en gezien het bovenstaande zal het dan ook weinig waardevol zijn om het hydroxyproline-gehalte te bepalen in het vruchtwater als antenatale maat voor groeivertraging.

In sectie 2.2 en publicaties II en III worden twee problemen belicht. In publicatie II werd de incidentie van 6 veel voorkomende neonatale complicaties (asphyxie, acidose, hypothermie, hyperviscositeit, hypoglycemie en hyperbilirubinemie) onderzocht in een groep van 500 à terme pasgeborenen. De onderzoeksgroep werd onderverdeeld naar de plaats van het geboortegewicht (voor de zwangerschapsduur) en de ponderal index op de percentielcurven. De resultaten lieten zien dat een kleine ponderal index een grotere voorspellende waarde heeft ten aanzien van het optreden van neonatale complicaties (met uitzondering van hyperbilirubinemie) dan een ondergewicht voor de zwangerschapsduur (gedefinieerd als een geboortegewicht beneden de 10e percentiel). Binnen de groep van pasgeborenen met een te laag geboortegewicht voor de zwangerschapsduur toonden vooral diegenen die gedisproportioneerde groeivertraging in utero doormaakten (vastgesteld aan de hand van een kleine ponderal index) neonatale complicaties. Dit laatste verschijnsel werd nader onderzocht in publicatie III in een groep van à terme pasgeborenen met een nog lager geboortegewicht voor de zwangerschapsduur (beneden de 2.3 percentiel). Wederom toonden de gedisproportioneerde pasgeborenen meer neonatale problemen dan de geproportioneerde pasgeborenen. Uit beide studies kan de conclusie worden getrokken dat een kleine ponderal index vooral die à terme pasgeborenen (met een laag geboortegewicht voor de zwangerschapsduur) selecteert die een

hoog risico lopen om neonatale complicaties te ondervinden.

In sectie 2.3 en publicaties IV en V wordt de lichamelijke groei in de eerste levensjaren van een groep van 25 normale à terme pasgeborenen vergeleken met een groep van 25 à terme pasgeborenen met klinische tekenen van gedisproportioneerde intrauteriene groeivertraging, vastgesteld aan de hand van een kleine ponderal index bij de geboorte. Beide groepen kinderen toonden geen opvallende klinische problemen in de neonatale periode behoudens de aanwezigheid van groeivertraging, tevens waren de groepen goed vergelijkbaar qua leeftijd, geslacht, rangorde in het gezin en sociale klasse. Bij deze studie werden het gewicht, de lengte, de schedelomtrek, de huidplooidikte en de uitrijping van het skelet als parameters bestudeerd. Hoewel de gedisproportioneerde groep kinderen in de eerste 6 levensmaanden een duidelijke inhaalgroei liet zien, hadden deze kinderen op 3 jarige leeftijd nog steeds een duidelijke achterstand in gewicht (naar lengte), een verminderde huidplooidikte en een kleinere schedelomtrek in vergelijking met de controle groep. Hoewel de gedisproportioneerde pasgeborenen bij de geboorte een duidelijke vertraging in de uitrijping van het skelet hadden, benaderde op 3 jarige leeftijd hun gemiddelde skeletrijping nagenoeg die van de controle groep. Echter, de kinderen uit de onderzoeksgroep wier lengte bij 3 jaar nog onder de 10e percentiellijn lag, hadden een vertraagde skeletrijping ten opzichte van hen die een lengte boven de 10e percentiellijn hadden bereikt. Uit deze onderzoeken kon worden geconcludeerd dat pasgeborenen met gedisproportioneerde intrauteriene groeivertraging minder goed groeien dan normale pasgeborenen ondanks het feit dat er in de eerste 6 levensmaanden inhaalgroei optreedt. Zij gedragen zich in dit opzicht als de hele groep van kinderen met een laag geboortegewicht voor de zwangerschapsduur. Dit is waarschijnlijk te verklaren uit de aanwezigheid van veel kinderen met gedisproportioneerde groeiver-

traging binnen de groepen pasgeborenen met een laag geboortegewicht voor de zwangerschapsduur welke door andere onderzoekers werden nagezien.

In 2.4 en publicaties VI en VII wordt het gedrag, het neurologisch functioneren en de taalontwikkeling van de in publicaties IV en V beschreven onderzoeksgroep geanalyseerd op de leeftijd van 3 jaar. Het gedrag werd bestudeerd met behulp van de vragenlijst van Richman en Graham (B.S.Q.) en door middel van een gestandaardiseerde gedragsobservatie (B.O.R.). Gedragsproblemen kwamen in grote getale voor bij de groep met intrauteriene groeivertraging. Er werden hierbij 2 karakteristieke gedragspatronen waargenomen: waar de ene groep kinderen hyperactiviteit en concentratiestoornissen aan de dag legde, toonde de andere groep kinderen vaak een opvallend angstig gedrag. Neurologisch dysfunctioneren en een vertraagde taalontwikkeling werden in ongeveer éénderde van de kinderen met intrauteriene groeivertraging vastgesteld. Een vertraagde taalontwikkeling ging veelal samen met opvallende gedragsproblemen, een door logopedisten veel gezien probleem. Ook neurologisch dysfunctioneren correleerde goed met een vertraagde taalontwikkeling en met het bestaan van gedragsproblemen. Het geheel wijst erop dat intrauteriene groeivertraging vaak uitmondt in de aanwezigheid van tekenen van cerebraal dysfunctioneren bij na-onderzoek op 3 jarige leeftijd en dat op die leeftijd gedragsproblemen, neurologisch dysfunctioneren en een vertraagde taalontwikkeling onderling vergelijkbaar zijn als indicatoren voor het bestaan van cerebrale dysfunctie. Het zal duidelijk zijn dat het vroegtijdig vaststellen van het bestaan van cerebraal dysfunctioneren bij het kind met intrauteriene groeivertraging door middel van de beschreven technieken van veel belang is.

In het kort kan aan de hand van de verrichte onderzoeken gezegd worden dat pasgeborenen met gedisproportioneerde intra-

uteriene groeivertraging een hoog risico lopen om neonatale complicaties te krijgen (zoals asphyxie, acidose, hypoglycemie, hyperviscositeit en hypothermie), minder goed te groeien na de geboorte en om cerebraal suboptimaal te functioneren op 3 jarige leeftijd. Het is aanbevelenswaardig bij de geboorte niet alleen het gewicht te relateren aan de zwangerschapsduur, maar ook de ponderal index te berekenen: een kleine waarde (b.v. beneden de 10e percentiel voor de zwangerschapsduur) moet onafhankelijk van het geboortegewicht van de pasgeborene als een reden worden beschouwd om het kind in te delen bij de groep van pasgeborenen met een verhoogd risico.

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Publication I

Intrauterine malnutrition and urinary hydroxyproline excretion.
F.J. Walther and L.H.J. Ramaekers: Journal of Perinatal Medicine 8 (1980), 272-277.

Publication II

The ponderal index as a measure of the nutritional status at birth and its relation to some aspects of neonatal morbidity.
F.J. Walther and L.H.J. Ramaekers: Journal of Perinatal Medicine 10 (1982), 42-47.

Publication III

Neonatal morbidity of S.G.A. infants in relation to their nutritional status at birth.
F.J. Walther and L.H.J. Ramaekers: Acta Paediatrica Scandinavica 71 (1982), 437-440.

Publication IV

Growth in early childhood of newborns affected by disproportionate intrauterine growth retardation.
F.J. Walther and L.H.J. Ramaekers: Acta Paediatrica Scandinavica 71 (1982), 651-656.

Publication V

Skeletal maturity at birth and at the age of 3 years of infants malnourished in utero.
F.J. Walther, L.H.J. Ramaekers, J.M.A. van Engelshoven: Early Human Development 5 (1981), 139-143.

Publication VI

Developmental aspects of subacute fetal distress: Behaviour problems and neurological dysfunction.
F.J. Walther and L.H.J. Ramaekers: Early Human Development 6 (1982), 1-10.

Publication VII

Language development at the age of 3 years of infants malnourished in utero.
F.J. Walther and L.H.J. Ramaekers. Neuropaediatrics 13 (1982), 77-81.

PUBLICATION I: INTRAUTERINE MALNUTRITION AND URINARY HYDROXYPROLINE EXCRETION

Summary

The purpose of this study was to investigate if the excretion of hydroxyproline in the first urine of newborns could be used as a biochemical parameter for the diagnosis of intrauterine malnutrition preliminary to investigation of amniotic fluid. Hydroxyproline in the urine is considered a reliable index of bone collagen metabolism and correlates well with skeletal growth which is retarded in intrauterine malnutrition (12).

A precisely defined diagnosis of malnutrition and its severity is necessary first of all. In order to quantify the degree of malnutrition of newborns the deviation of the ponderal index (100 x weight in grams/length in centimeters)^3) from 'normal' (defined as the 50 centile of the data of Lubchenco et al. (9)) was used. By chemical analysis the total hydroxyproline excretion in the first urine sample passed after birth was determined as well as the creatinine excretion. As creatinine excretion is correlated with body size and muscle mass, the total hydroxyproline (mmol/l) / creatinine (mmol/l) or THP/Cr. ratio was used instead of the absolute values of the total hydroxyproline excretion as it gives more consistent results for subjects of the same biological age. Single samples of urine could be used because they show a good correlation with 24-hour collections of urine.

50 Selected normal and malnourished term infants were investigated, all were Caucasian babies without congenital malformations, congenital infections, and chromosomal abnormalities, whereas small-for-dates due to chronic fetal distress and genetically determined small-for-dates were excluded. No correlation

between the degree of intrauterine malnutrition (defined as the deviation of the ponderal index from 'normal growth') and the THP/Cr. ratio could be established (Fig. 1). Other studies, not defining the degree of intrauterine malnutrition, show a considerable overlap between normal and malnourished term infants. This study proves that urinary hydroxyproline excretion cannot be used clinically as a measure of intrauterine malnutrition of the newborn, probably because intrauterine growth is retarded already under normal conditions in the last trimester (5). The normal range of urinary hydroxyproline excretion being already wide, starvation does not add a measurable and significant decrease to the hydroxyproline excretion.

Introduction

Both amniotic fluid and urine of newborns contain hydroxyproline, an amino-acid related to the collagen metabolism and particularly the collagen matrix. Phases of rapid growth of the human body are accompanied by a high collagen turnover resulting in an increased excretion of hydroxyproline in the urine, whereas malnourishment and retarded growth lead to a diminished output (11,15).

In normal pregnancy the total hydroxyproline/creatinine (THP/Cr.) ratio in amniotic fluid shows a rise around 15-19 weeks of gestation followed by a prolonged fall towards term (13). This coincides with the rapid increase in length of the fetus.

Theoretically the THP/Cr. ratio in amniotic fluid might be used as a biochemical measure of assessing intrauterine growth. This was investigated in a preliminary report by Bissender et al. (2) showing significant lower amniotic THP values in European pregnancies with intrauterine malnourished infants in comparison with pregnancies with normally grown babies. But was there was a considerable overlap of the values, the clinical use of THP estimation without further evaluation was considered to be

limited.

Because amniotic fluid is not readily available for research purposes, the first urine after birth can be used instead. This was done by Younoszai et al. (16). They could not demonstrate significant differences in the first specimen of urine after birth in normal term infants and malnourished newborns. No data on the degree of malnourishment are available however.

Intrauterine malnutrition is the most frequent cause of S.G.A., and these infants are usually recognizable clinically as being wasted and showing disproportional growth. This dissociation of weight and length can be objectively determined by the use of the Ponderal Index (P.I.) of Rohrer (100 x weight in grams/(length in centimeters)^3). By comparison of the P.I. with the 50 centile of the data of Lubchenco et al. (9) (arbitrarily considered as being the index of appropriate normal growth) the degree of intrauterine malnutrition can be quantified according to Roord and Ramaekers (11). Furthermore these authors concluded, that though the ponderal index can be used as a measure of malnutrition, birthweight alone is not a correct parameter for the definition of starvation. Therefore the malnourished newborn can have a weight well above the small-for-gestational age (S.G.A.) borderline of the 10th centile and still be undernourished.

In this study we tried to establish a correlation between the degree of intrauterine malnutrition and the THP/Cr. ratio in the first urine voided by 50 selected term newborns. This in order to find out if hydroxyproline excretion can be used as a biochemical parameter for diagnosis of intrauterine malnutrition by investigating the amniotic fluid in a later trial.

Material and Methods

The patients consisted of 50 newborn singletons of both sexes and from all social classes, with a nutritional state varying from

severe malnourishment to normal growth. They were born at a gestational age of 38 or more weeks. Those showing signs of wasting were admitted to the Department of Neonatology for a variety of reasons, the others were healthy newborns of the Obstetric Department. Gestational age was calculated from the first day of the last menstrual period and verified by the Dubowitz score, those showing a difference of more than one week were excluded from the study.

Excluded were non-Caucasians and infants with congenital malformations, congenital infections, chromosomal abnormalities and small-for-dates due to chronic fetal distress (5). Rohrer's ponderal index ($100 \times W/L^3$) was determined and the deviation from 'normal' (50 centile of the data of Lubchenco et al. (9)) calculated according to Roord and Ramaekers (11).

Immediately after birth first urine samples were collected in plastic bags, which were emptied as soons as they contained 15 ml. of urine, a quantity always met at the first voidance. Urine was stored frozen at $-10^{o}C$. Creatinine in the urine was determined by the classical method of Jaffé after dialysis to remove non specific chromogens of low molecular origin.

Total urinary hydroxyproline was estimated as described by Goverde and Veenkamp (3), which method is in good agreement with that of Prockop-Kivirikko (7). The ratios of total hydroxyproline (mmol/l)/creatinine (mmol/l) were calculated. Single samples were used as Younoszai et al. (17) and Howells et al. (6) showed a good correlation between THP/Cr. ratios in 24-hours collections and in random urine samples. 24-Hour sampling seemed therefore unnecessary.

Results

In analyzing the 50 newborns proved to show a continuum of normal growth to an increasing degree of wasting whereas 3 newborns also

showed postmature characteristics (Clifford* stages I/III).

The mean and range for weight and height are given in Tab. I, the distribution on the percentile charts of the Rohrer index (9) in Tab. II. Fig. 1 represents the correlation between deviation from 'normal' ponderal index (50 centile for the individual gestational week) and the THP/Cr. ratio in the first urine voided after birth. No significant relationship between those two parameters could be established (all points were used in calculating the regression equation: $Y = 0.115-0.038X$; $r = -0.141$, $n = 50$, N.S.). Also no correlation was found between the absolute THP values or THP/Cr. ratio and weight, length and body surface at birth. Girls tended to a lower THP/Cr. ratio than boys (0.108 with a standard deviation of $\pm$ 0.037 vs. 0.135 $\pm$ 0.066), though

Table I Mean and range of weight and length of the study group.

	Weight g		Length cm	
	mean	range	mean	range
Study group	3071	1630-4130	50.3	43.1-55.0

Table II Distribution of the study group on the percentile charts of the Rohrer index.

Percentile ranges	Number of studied newborns
P50-75	6
P25-50	17
P10-25	16
P < 10	11
Total	50

*Clifford SH (1954): Postmaturity - with placental dysfunction. J. Pediatr. 44: 1-13.

these differences were not statistically significant ($P > 0.05$). The mean THP/Cr. ratio of the whole group amounted to 0.124 with a range of 0.040-0.331 and a standard deviation of 0.055.

Discussion

The THP/Cr. ratio has been shown to be related to collagen turnover and to reflect the rate of growth in children. The largest amounts of hydroxyproline are excreted with the urine during the first three months of life. Thereafter it falls quickly till 12 months of age followed by a much slower decrease until pubertal growth spurt (4, 14).

The ratio of total hydroxyproline/creatinine is used instead of the absolute values of the total urinary hydroxyproline excretion because it gives more consistent results for subjects of the same biological age, as creatinine excretion is correlated with

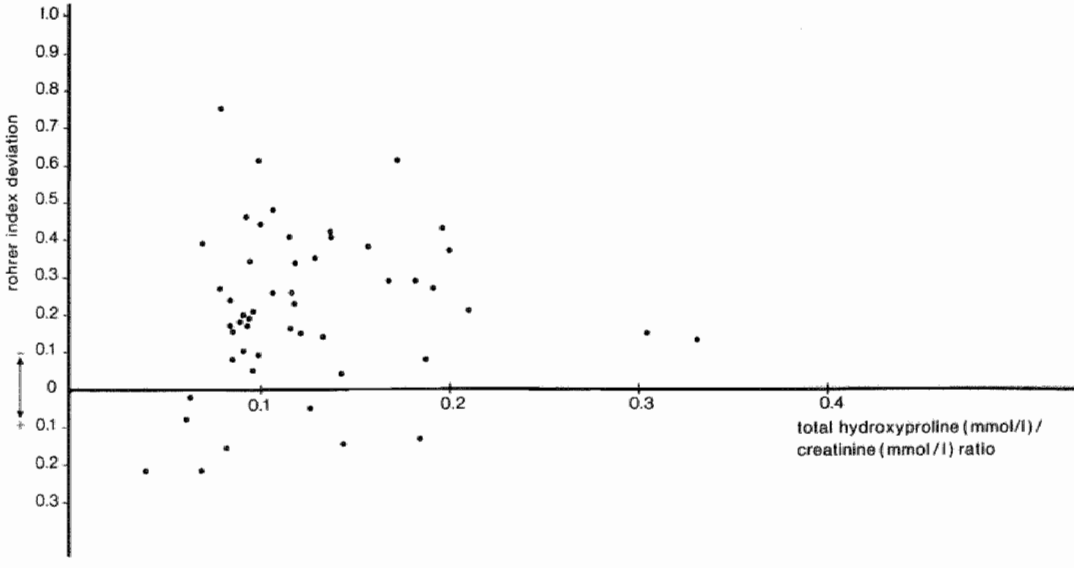

Fig. 1 Correlation between Rohrer index deviation from 'normal' and total hydroxyproline (mmol/l)/creatinine (mmol/l) ratio in the first urine passed by newborns.

body size and muscle mass (1). Whereas in children over 6 months of age the major portion of urinary hydroxyproline is peptide-bound and only 5% or less is in the free form, infants during the first three months of life excrete about a third of the total hydroxyproline in the free form (4).

Klujber et al. (8) found that premature infants, intrauterine malnourished term infants and normally grown infants excreted about the same proportion of free hydroxyproline during the first three weeks of life, which means that total urinary hydroxyproline measurements can be used in that period.

Although our values are in good agreement with the values found by Younoszai et al. (16) we could not find any correlation between the degree of growth retardation and THP excretion. The explanation for this is probably the fact that intrauterine growth is retarded under normal circumstances in the last trimester according to Gruenwald (5). The normal range of urinary THP excretion being already wide, starvation does not add a measurable and significant decrease to THP excretion.

Other parameters have to be searched for, as prenatal diagnosis of intrauterine malnutrition by means of biochemical analysis of amniotic fluid seems important. More promising may be the amniotic or urinary 3-methyl-histidine excretion. This amino-acid is almost exclusively present in skeletal muscle proteins and is excreted without further metabolism or recycling during their catabolism (10) in rats. However, the difficult quantitative estimation of this amino-acid hampers its clinical research up till now.

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PUBLICATION II: THE PONDERAL INDEX AS A MEASURE OF THE NUTRITIONAL STATUS AT BIRTH AND ITS RELATION TO SOME ASPECTS OF NEONATAL MORBIDITY.

Summary

The purpose of this study was to investigate if the ponderal index might be a better measure to predict neonatal morbidity than birthweight for gestational age. The ponderal index (100 x W/L^3) assesses whether an infant appears relatively 'fat' or 'thin' at birth by quantification of the dissociation of weight and length and is of great help to recognize wasted infants irrespective of their distribution on the percentile lines of birthweight for gestational age. Except that the ponderal index is more informative about the nutritional status at birth, it is relatively independent of race, sex, birthrank, and gestational age at term (11). Therefore the ponderal index is an easier tool for rapid diagnosis of intrauterine malnutrition at birth than birthweight for gestational age. The relation between the ponderal index and neonatal morbidity and between birthweight and neonatal morbidity was studied in a group of 500 term infants of various birthweight. The distribution of the infants by birthweight differed significantly from the distribution by ponderal index (Tab. I): whereas their average birthweight centred around the 25th percentile (7), their average ponderal index centred close by the 45th percentile (11). One third of the S.G.A. infants and 8% of the A.G.A. infants were wasted. 6 Common neonatal problems were investigated: asphyxia, acidosis, hypoglycemia, hypothermia, hyperviscosity and hyperbilirubinemia. Asphyxia, acidosis, hypoglycemia, hypothermia, and hyperviscosity were

significantly more frequently diagnosed in (wasted) infants with a small ponderal index, (Tab. II), whereas only hypoglycemia, hypothermia, and hyperviscosity could be related to a low birthweight for gestational age (Tab. III). Especially the combination of wasting and underweight pointed to a high incidence of neonatal morbidity (Tab. IV). Hyperbilirubinemia was rare in both wasted and underweight infants.

It seems warrantable to conclude that like birthweight the ponderal index is a reliable measure of neonatal morbidity. Therefore the calculation of the ponderal index at birth deserves a place beside the estimation of birthweight for gestational age.

Introduction

Intrauterine malnutrition is generally defined by low birthweight for a gestational age calculated from the last normal period and corroborated by clinical assessment of the infant at birth (16). However, not all infants affected by intrauterine malnutrition will be included in such a definition as an unknown percentage of newborns whose birthweight does not fall below the normal for gestational age, have not achieved their full growth potential (3). Clinically these infants will be recognized by manifest soft tissue loss, usually called 'wasting'.

To facilitate the diagnosis of intrauterine malnutrition at birth it is useful to incorporate body length in the assessment and to calculate Rohrer's ponderal index ($100 \times W/L^3$) which assesses whether an infant appears relatively 'fat' or 'thin' by quantification of the dissociation of weight and length (3, 12). Wasted infants will show a relatively small ponderal index irrespective of their distribution on the percentile lines of birthweight for gestational age. Lubchenco et al. (9) and Miller and Hassanein (11) provided standard curves of the ponderal index (P.I.) for gestational age. Since Gruenwald (3) widely explained

its benefits several authors have used the P.I. as criterion to define the state of nutrition of their study groups. These studies have demonstrated that the P.I. at birth is correlated with skinfold thickness (11), skeletal retardation (13, 17), postnatal growth (1, 17) and behaviour problems and neurological dysfunction at pre-school age (18).

It is known that small-for-gestational age (S.G.A.) infants (whose birthweight is below the 10th percentile for gestational age) have a higher incidence of asphyxia, hypoglycemia (19), hypothermia (14), and hyperviscosity (4, 19) in the neonatal period. Unlike birthweight the relation between the P.I. (as a quantitative measure of the nutritional status at birth) and neonatal morbidity has not yet been properly evaluated. For that purpose the incidence of 6 common neonatal problems (asphyxia, acidosis, hypothermia, hypoglycemia, hyperviscosity, and hyperbilirubinemia) was examined in a group of 'unselected' term infants in relation to birthweight and to P.I. distribution.

Material and Methods

The subjects in this study consisted of 500 consecutive live-born infants admitted to the neonatal ward directly after birth. All were Caucasian singletons born at a gestational age between 38 and 42 weeks, as verified by the Dubowitz score (2). Excluded were infants of diabetic mothers, infants with Rh or ABO hemolytic disease, and infants with fetal diseases (congenital infections and anomalies, chromosomal aberrations). 55% Of the infants were admitted for observation after an artificial delivery, 22% because of signs of intrauterine malnutrition, 8% because of overweight, and 15% for a variety of reasons.

Weight and length were measured after birth using methods previously described (12). Of each infant the percentile of birthweight for gestational age was established allowing for sex

and birth order (7). Furthermore the P.I. (100 x weight in grams/ length^3 in cm) was calculated for each infant and its distribution on the percentile charts of Miller and Hassanein (11) was established. The next information of all infants was collected: Apgar scores at 1 and 5 minutes after birth; arterial umbilical pH; rectal temperature at admission; blood glucose levels at 1, 2, 3, 6, 12, 24 and 48 hours after birth; venous haematocrit levels if capillary haematocrit values from a pre-warmed heel amounted to 70% or more at 1 and/or 3 hours after birth (19); and serum bilirubin levels in case of neonatal jaundice. The variables assessed in this study were defined as follows. Neonatal asphyxia was diagnosed in infants who had an Apgar score of 0-3 at 1 and/or 5 minutes and required at least one minute of positive pressure ventilation before respiration occurred. Acidosis was defined as an arterial umbilical pH < 7.09 (5). Hypothermia was defined as an admission rectal temperature < 35.5°C. Hypoglycemia was defined as a blood sugar concentration ≤ 1.6 mmol/l. Hyperviscosity was defined as a venous haematocrit ≥ 65%. Hyperbilirubinemia was defined as a total bilirubin concentration > 200 µmol/l. As a routine clamping of the umbilical cord took place before 1 minute after birth of the infants. All vital problems were managed by a paediatrician in the delivery room. All infants in the study were subjected to an early feeding practice. The distribution of discrete variables was compared by chisquare.

Results

The distribution of the infants by birthweight for gestational age and by P.I. is presented in Tab. I. The distribution by birthweight differs significantly from the distribution by ponderal index. Whereas 119 of the 500 (23.8%) infants had a birthweight below the 10th percentile for gestational age (and were

S.G.A.), only 80 of the 500 (16.0%) infants had a P.I. below the 10th percentile (and were wasted). As 46 of the 500 (9.2%) infants had both a birthweight and a P.I. below the 10th percentiles, there exists a firm correlation between these two parameters (X^2 = 59.639, DF = 1, $p < 0.0005$).

73/119 (61.3%) S.G.A. infants had a P.I. on or above the 10th percentile and were not severely wasted. 34 Infants had a P.I. below the 10th percentile and a birthweight on or between the 10th and 90th percentiles, indicating that 8.1% of the A.G.A. (appropriate-for-gestational age) infants were clinically wasted.

Tab. II shows that asphyxia (X^2 = 12.921, DF = 5, $p < 0.025$), acidosis (X^2 = 11.674, DF = 5, $p < 0.05$), hypoglycemia (X^2 = 14.671, DF = 5, $p < 0.025$), hypothermia (X^2 = 37.221, DF = 5, $p < 0.0005$), and hyperviscosity (X^2 = 17.235, DF = 5, $p < 0.005$) were significantly more often diagnosed in infants with a small P.I. A statistically significant correlation between the P.I. and hyperbilirubinemia was absent. As 11 of the 42 infants with asphyxia also presented acidosis, a significant correlation between acidosis and asphyxia could be established (X^2 = 15.845, DF = 1, $p < 0.005$).

Infants whose birthweight for gestational age is low, had a higher incidence of hypoglycemia (X^2 = 12.327, DF = 5, $p < 0.05$), hypothermia (X^2 = 33.484, DF = 5, $p < 0.0005$) and hyperviscosity (X^2 = 44.680, DF = 5, $p < 0.0005$), (Tab. III).

Asphyxia, acidosis, and hyperbilirubinemia were not significantly related to S.G.A. infants, though the incidence of asphyxia was slightly higher in S.G.A. infants.

One or more of the 6 investigated neonatal problems were diagnosed in 57/119 (47.9%) S.G.A. infants, in 41/80 (51.2%) infants with a P.I. below the 10th percentile, and in 30/46 (65.2%) infants whose birthweight and P.I. fell below the 10th percentiles.

Tab. IV points out that in general infants with a birthweight and a P.I. below the 10th percentiles showed more often neonatal problems than wasted A.G.A. infants and non-wasted S.G.A. infants. Hyperviscosity is an exception to this rule as it was more often seen in both wasted and non-wasted S.G.A. infants. Hyperbilirubinemia centred around the 50th percentiles of both birthweight and the ponderal index and its incidence was not increased in any of the 3 subgroups defined above.

Table I Distribution of the study group on the percentile charts of birthweight and of the ponderal index (percentages)

P.I. \ Birthweight	< 10	10–25	26–50	51–75	76–90	> 90	Total (100%)
< 10	46	22	5	5	1	1	80 (16.0%)
10–25	24	23	16	9	1	1	74 (14.8%)
26–50	29	37	33	30	7	2	138 (27.6%)
51–75	15	25	20	33	23	16	132 (26.4%)
76–90	3	4	7	8	12	8	42 (8.4%)
> 90	2	3	2	8	7	12	34 (6.8%)
Total (100%)	119 (23.8%)	114 (22.8%)	83 (16.6%)	93 (18.6%)	51 (10.2%)	40 (8.0%)	500

Table II Distribution of neonatal morbidity on the percentile blocks of the ponderal index (percentages of the percentile blocks)

P.I. / Neonatal morbidity	< 10	10–25	26–50	51–75	76–90	> 90	Total
	n = 80	n = 74	n = 138	n = 132	n = 42	n = 34	n = 500
Asphyxia	14 (17.5)	6 (8.1)	11 (8.0)	9 (6.8)	2 (4.8)	0 (0)	42 (8.4)
Acidosis	15 (18.7)	7 (9.4)	10 (7.2)	10 (7.6)	3 (7.1)	1 (2.9)	46 (9.2)
Hyperviscosity	10 (12.5)	9 (12.2)	9 (6.5)	1 (0.7)	1 (2.4)	2 (5.9)	32 (6.4)
Hypoglycemia	7 (8.7)	1 (1.3)	2 (1.4)	4 (3.0)	4 (9.5)	0 (0)	18 (3.6)
Hypothermia	19 (23.7)	5 (6.7)	7 (5.1)	6 (4.5)	1 (2.4)	0 (0)	38 (7.6)
Hyperbilirubinemia	4 (5.0)	0 (0)	10 (7.2)	11 (8.3)	3 (7.1)	0 (0)	28 (5.6)

Table III Distribution of neonatal morbidity on the percentile blocks of birthweight for gestational age (percentages of the percentile blocks)

Neonatal morbidity \ Birthweight	< 10	10–25	26–50	51–75	76–90	> 90	total
	n = 119	n = 114	n = 83	n = 93	n = 51	n = 40	n = 500
Asphyxia	17 (14.3)	6 (5.3)	9 (10.8)	4 (4.3)	3 (5.9)	3 (7.5)	42 (8.4)
Acidosis	15 (12.6)	12 (10.5)	6 (7.2)	3 (3.2)	6 (11.8)	4 (10.0)	46 (9.2)
Hyperviscosity	23 (19.3)	4 (3.5)	3 (3.6)	1 (1.1)	1 (2.0)	0 (0)	32 (6.4)
Hypoglycemia	5 (4.2)	4 (3.5)	2 (2.4)	2 (2.1)	0 (0)	5 (12.5)	18 (3.6)
Hypothermia	22 (18.5)	11 (9.6)	2 (2.4)	2 (2.1)	1 (2.0)	0 (0)	38 (7.6)
Hyperbilirubinemia	6 (5.0)	4 (3.5)	5 (6.0)	9 (9.7)	2 (3.9)	2 (5.0)	28 (5.6)

Table IV Neonatal morbidity in 3 subgroups (percentages)

Neonatal morbidity	P.I. and birthweight < 10th percentiles	P.I. < 10th percentile and birthweight ⩾ 10th percentile	Birthweight < 10th percentile and P.I. ⩾ 10th percentile
	n = 46	n = 34	n = 73
Asphyxia	10 (21.7)	4 (11.8)	7 (9.6)
Acidosis	11 (23.9)	4 (11.8)	4 (5.5)
Hyperviscosity	8 (17.4)	2 (5.9)	15 (20.5)
Hypoglycemia	4 (8.7)	3 (8.8)	1 (1.4)
Hypothermia	16 (34.8)	3 (8.8)	6 (8.2)
Hyperbilirubinemia	3 (6.5)	1 (2.9)	3 (4.1)

Discussion

Except the indicated limitations, assessment of fetal growth by means of birthweight for gestational age regularly throws up problems in daily practice. For example insufficient information about the gestational age may hamper the interpretation of birthweight, whereas infants of different race, sex, and birthrank cannot be compared without the consultation of different standard graphs of intrauterine growth. The use of the ponderal index may then be of great help as it is relatively independent of race,

sex, birthrank, and gestational age at term (11). As the P.I. also points to wasted infants whose birthweight is appropriate for gestational age (about 8% in this study) and quantifies intrauterine malnutrition, its advantages are obvious in daily practice. However, birthweight for gestational age has yielded important information about the relationship between intrauterine growth retardation and neonatal morbidity and mortality. It continues therefore to deserve its place in the classification of infants at birth. In need of more information about the nutritional status at birth it is advantageous to consider the P.I.

Of the six neonatal problems assessed in this study only hypoglycemia has been analysed in relation to the P.I. before. Járai et al. (6) investigated a mixed group of preterm, term, and postterm S.G.A. infants using different indices of body proportions and pointed to the significance of soft tissue wasting (rather than low birthweight for gestational age itself) in the development and diagnosis of neonatal hypoglycemia. The same conclusion emerges from this study. But it also shows that hypoglycemia occurred often in overweight infants (P.I. > 75th percentile and/or birthweight >90th percentile) whose mothers were free from diabetes. The cause of this phenomenon remained unclear.

Generally speaking it can be said that the P.I. is equal to or surpasses birthweight for gestational age as a tool to predict neonatal problems like asphyxia, acidosis, hypoglycemia, and hypothermia. Though hyperviscosity is more common in infants with a small P.I., it occurs especially in those infants whose birthweight falls below the 10th percentile. A proper explanation of this fact is unknown to us and will need further study.

Though low values of the arterial umbilical pH correlated well with a low Apgar score (as shown by Huisjes and Aarnoudse in a recent study (5)) and the necessity of positive pressure ventila-

tion, this relation was not complete as only one fourth of the asphyxia cases presented with severe acidosis and the other way round. This phenomenon has been laid down in a publication of Litschgi et al. (8) who described that especially the combination of a low Apgar score and acidosis resulted in an increased incidence of neurological morbidity. As this combination was mostly diagnosed in the underweight infants who were wasted, this group will be at high risk of developmental problems as a result of this problem. Hyperbilirubinemia is relatively rare in wasted and underweight infants. This is probably due to an advanced stage of functional maturity of the liver post partum brought on by a large blood volume and a higher haematocrit (15).

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PUBLICATION III: NEONATAL MORBIDITY OF S.G.A. INFANTS IN RELATION TO THEIR NUTRITIONAL STATUS AT BIRTH

Summary

46 Consecutively born term infants with a birthweight ≤ the 2.3 percentile for gestational age were divided into two groups according to their nutritional status at birth quantified by the ponderal index (100 x weight/length^3). Though all infants had a ponderal index below the 50th percentile, those with a ponderal index below the 3rd percentile (about half of the study group) were more frequently affected by asphyxia, hypoglycemia, hypothermia, and hyperviscosity than their more proportionally grown counterparts. On this account the identification of disproportionally grown small-for-gestational age infants by using the ponderal index as a yardstick of the nutritional status at birth, is necessary because they constitute a high-risk group among small-for-gestational age infants.

Introduction

Small-for-gestational age (S.G.A.) infants are anything but homogeneous in their physical appearance at birth. Some are of normal length but look wasted and are therefore disproportionally small, while others are proportionally small. The former infants probably experienced growth retardation during the later weeks of intrauterine life, whereas the latter ones were affected during the whole last trimester. Gruenwald (1) introduced the terms subacute and chronic fetal distress to describe disproportionate and proportionate intrauterine growth retardation at birth. Recently Davies et al. (2) established that disproportionally grown S.G.A. infants grow more rapidly after birth than propor-

tionally grown S.G.A. infants, and emphasized the importance of the nutritional status at birth for prognostic purposes.

As the incidence of both forms of intrauterine growth retardation is not wel known and as the incidence of neonatal morbidity may be different in disproportionally and proportionally grown S.G.A. infants, we studied a group of S.G.A. infants whose nutritional status at birth was determined by use of the ponderal index (P.I.).

Subjects and Methods

Studied were 46 consecutively born term infants whose weight was on or below the 2.3 percentile (2 S.D. from the mean) for gestational age, allowing for sex and birth order (3) and for maternal height (4). All were Caucasian and singletons. None had any congenital malformation, chromosomal anomaly, or intrauterine infection. The infants were studied prospectively. Weight, length and head circumference were measured after birth using methods previously described (5).

The ponderal index (100 x weight in grams/length^3 in cm) was calculated for each infant and two groups were identified using the distribution of the P.I. on the percentile charts of Miller and Hassanein (6): group 1 included 23 disproportionally grown S.G.A. infants whose P.I.'s were below the 3rd percentile for gestational age, group 2 included 21 proportionally grown S.G.A. infants whose P.I.'s exceeded the 10th percentile for gestational age. Two infants whose P.I. was between the 3rd and the 10th percentiles were excluded from the ultimate analysis.

Hypertensive disorders (defined by the presence of a diastolic blood pressure exceeding 90 mmHg) and smoking habits of all mothers were registered. The next data about the infants were collected: sex; birth rank; gestational age in completed weeks from the mother's last normal menstrual period and verified by

the Dubowitz score (7); the mode of delivery and the presence of acute fetal distress at antepartum monitoring; placental weights after removal of the umbilical cord and the membranes.; Apgar scores at 1 and 5 min. after birth and the presence of signs of postasphyxial respiratory distress; arterial umbilical pH; rectal temperature at admission to the neonatal ward; blood glucose levels at 1, 2, 3, 6, 12, 24 and 48 hours after birth; venous haematocrit levels if capillary haematocrit values from a pre-warmed heel amounted to 70% or more at 1 and/or 3 hours after birth (8); and serum bilirubin if neonatal jaundice occurred.

Asphyxia was defined as an Apgar score of 0-3 at 1 min. and/or an arterial umbilical pH below 7.09 (9). Hypoglycemia was defined as a blood sugar concentration below 1.6 mmol/l, hyperviscosity as a venous haematocrit exceeding 65%, hypothermia as an admission temperature $\leq 35.0^{\circ}C$, and hyperbilirubinemia as a total bilirubin concentration > 200 µmol/l. As a routine clamping of the umbilical cord took place before 1 minute after birth. Vital problems were managed by a paediatrician in the delivery room. All infants in the study were subjected to an early feeding practice.

Statistical significance of differences between means was assessed by the Student's t-test. The distribution of discrete variables in the two groups was compared by chi-square.

Results

Twenty-three (50%) of the S.G.A. infants were disproportionally grown (group 1) and 21 (46%) proportionally grown (group 2). Both groups showed a slight preponderance of boys over girls: in group 1 the ratio boys/girls was 12 : 11 and in group 2 12 : 9. First-borns preponderated over higher birth ranks in group 1 (16/23), but constituted a minority in group 2 (6/21), the difference is statistically significant ($p < 0.01$). Hypertensive disorders

Table 1 Mean values of growth parameters at birth in disproportionally (group 1) and proportionally (group 2) grown S.G.A. infants (standard deviation)

	Group 1 $n=23$	Group 2 $n=21$	p
Gestational age, wks	40.2 (1.1)	40.0 (1.1)	N.S.[a]
Weight, g	2337 (256)	2473 (160)	<0.001
Length, cm	48.1 (1.8)	46.9 (1.2)	<0.02
Ponderal index	2.09 (0.12)	2.38 (0.10)	<0.001
Head circumference, cm	32.7 (0.8)	32.7 (1.1)	N.S.
Placental weight, g	388 (62)	415 (74)	N.S.

[a] N.S.: not significant.

(23%) and smoking habits were comparable, the overall incidence of smoking during pregnancy was high (68%). Table 1 demonstrates that the disproportionally grown infants are lighter and longer than the proportionally grown infants at comparable mean gestational ages, whereas their mean head circumference measurements were comparable. In 56% of the disproportionate group and in 33% of the proportionate group placental weights were below the 5th percentile of gestational age ($p > 0.05$), mean placental weights did not differ significantly but were relatively low for gestational age (3). Placental insufficiency, defined as necrosis of more than 10% of the placental parenchyma, was diagnosed in 4 disproportionally grown infants and in none of the proportionate group ($p < 0.05$).

Artificial deliveries because of signs of acute fetal distress at monitoring occurred to the same extent in both groups (5/23 in group 1 and 3/21 in group 2). Asphyxia and consequential respiratory distress occurred more often in group 1 (7/23) than in group 2 (2/21), $p < 0.05$. The same applied for hypoglycemia (4/23 in group 1 and 0/21 in group 2, $p < 0.025$), hyperviscosity (7/23 in group 1 and 1/21 in group 2, $p < 0.025$) and hypothermia (6/23 in group 1 and 1/21 in group 2, $p < 0.05$). The mean values of the

concerning parameters (table 2) present the same picture, though mean arterial umbilical pH and capillary haematocrit values fail to reach statistical significance. Hyperbilirubinemia occurred in only 2 infants in each group.

Table 2 Means of parameters of neonatal morbidity in disproportionally (group 1) and proportionally (group 2) grown S.G.A. infants (standard deviation)

	Group 1 $n=23$	Group 2 $n=21$	p
Apgar at 1 min	6.3 (2.2)	7.8 (2.1)	<0.05
Apgar at 5 min	8.6 (1.2)	9.4 (0.8)	<0.02
Art. umbil. pH	7.19 (0.14)	7.23 (0.10)	N.S.
Lowest bloodsugar, mmol/l	2.3 (0.7)	2.8 (0.7)	<0.025
Temperature, °C	35.5 (0.7)	36.1 (0.4)	<0.005
Cap. haematocrit, %	68.5 (10.5)	64.7 (6.3)	N.S.

Discussion

Using a P.I. below the 3rd percentile for gestational age as a cut-off point about half of the S.G.A. infants in this study were disproportionally grown. This agrees well with the figure of 60% presented by Davies et al. (2) studying a group of infants with a birthweight below the 5th percentile for gestational age. In our study the mean P.I. of the proportionally grown infants is well below the 50th percentile and like Davies et al. (2) we are of the opinion that S.G.A. infants are mainly disproportionally grown. However, this may apply only to well nourished mothers in view of the study of Woods et al. (10) who demonstrated that in a South African population of undernourished mothers proportionally grown S.G.A. infants prevailed.

Miller and Hassanein (6) demonstrated that birthweight for gestational age alone fails to reflect the nutritional status of many newborns at birth and that the P.I. needs to be used as an additional yardstick. Using this classification our study provides evidence that disproportionally grown S.G.A. infants are at

a higher risk for neonatal complications than their proportionally grown counterparts: asphyxia, hypoglycemia, hypothermia, and hyperviscosity occurred more frequently in the disproportionate group. Despite early intervention the overall incidence of asphyxia in both groups was high in comparison with the figure of 0.5% in a large group of term infants presented by MacDonald et al. (11).

Probably due to the early feeding of the infants the overall incidence of hypoglycemia (9%) was much lower than the figure of 25% reported in S.G.A. infants in the early seventies (12, 13). In the whole group hyperviscosity (18%) occurred in about the same percentage as in the reports of Hakanson and Oh (14) and Wirth et al. (8) about S.G.A. infants, but the incidence in the disproportionate group (30%) was much higher. This may be correlated with the fact that intrauterine asphyxia was more often associated with disproportionate growth (15). As those infants showing hyperviscosity were treated by a plasma exchange transfusion (16) and as they probably have an advanced stage of functional liver maturity due to their larger blood volume (17), the incidence of hyperbilirubinemia was low.

Though placental insufficiency occurred more often in the group of disproportionally grown S.G.A. infants in this study, the origin of intrauterine growth retardation in both study groups often remained unknown. Extensive studies (18) have shown that primary failure of placental function is found in only a relatively small proportion of placentae from deprived fetuses. As the mean placental weights in both groups of infants are equally low, a deficient supply of oxygen or nutrients to the placenta seems a more attractive explanation. Possibly the high incidence of smoking during pregnancy is also of great importance as smoking has a direct toxic effect on the fetus (19).

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PUBLICATION IV: GROWTH IN EARLY CHILDHOOD OF NEWBORNS AFFECTED BY DISPROPORTIONATE INTRAUTERINE GROWTH RETARDATION

Summary

A group of term newborns affected by disproportionate intrauterine growth retardation as expressed by a small ponderal (100 x W/L^3), was followed-up with appropriate normally grown controls matched for age, sex, birth rank and social class. Despite catch-up growth during the first six months after birth the study group was still underweight-for-length with lower mean skinfold measures at the age of 3 years in comparison with the controls. This indicates that, despite its late onset in pregnancy, disproportionate intrauterine growth retardation continues to influence growth in early childhood.

Introduction

Several authors (1,2,3) have pointed out that intrauterine growth retardation (IUGR) cannot be diagnosed from birthweight and gestational age alone as these do not reflect the rates of growth in individual cases: some infants attain their birthweight by uniform slow growth, whereas others have experienced growth retardation in late pregnancy only. Unless there is some pathological or genetic condition within the fetus to account for its slow fetal growth rate, its cause must be considered to be an insufficient supply line (2). Clinically these infants can be divided into several types depending on the relative growth of the head and body length to the rest of the organs of the body (1,2,4,5,6). Whereas with adequate fetal growth weight, length

and head circumference are appropriate for gestational age, in mild and short-lived growth retardation only weight will be reduced due to loss of subcutaneous adipose tissue and muscle tissue (wasting). If weight and length are small but head circumference is appropriate moderate, prolonged fetal growth retardation exists. A reduction of weight, length and head circumference suggests severe, prolonged growth retardation. So small-for-gestational age (S.G.A.) infants are far from homogeneous in their physical appearance at birth. Even being born appropriate-for-gestational age (A.G.A.) does not necessarily indicate an optimal intrauterine growth rate as some A.G.A. infants have (like many S.G.A. infants) signs of recent weight loss (3).

It will be clear that a more reliable method of assessing fetal growth at birth is needed. A weight-for-length ratio eliminates the problem caused by large variations in length and weight within the group of S.G.A. infants when measuring relative body weight. Several authors have proposed Rohrer's ponderal index (100 x weight in grams/length^3 in cm) to that purpose (1,2,5). This index assesses whether an infant appears relatively 'fat' or 'thin' by quantification of the dissociation of weight and length. Infants who are small with respect to weight and length tend to have proportionate growth and their ponderal index is (near) normal. They experienced moderate or severe prolonged intrauterine growth retardation and their growth pattern has been described as chronic fetal distress (2), type 1 IUGR (4,5) or proportionate IUGR (6,7). Infants who are small with respect to weight only are disproportionally grown and their small ponderal index points to them being leaner, due in major part to less body fat as indicated by diminished skinfolds (3,8) and due to a lesser muscle bulk (9). They experienced mild IUGR in the last few weeks of pregnancy only and have been described as subacute fetal distress (2), type II IUGR (4,5), and disproportionate IUGR (7).

So by using the ponderal index an impression can be obtained about the duration and severity of IUGR, although this clinical classification is by no means infallible as there is or will be a considerable overlap both in the clinical picture and also in the etiology of the types of IUGR. At least the use of the ponderal index attempts to bring some order into the diagnosis of IUGR so that different studies will be able to define exactly what type of infant is considered (5).

Recently Davies et al. (10) demonstrated significantly higher growth rates (weight, length and head circumference) in severely wasted infants (ponderal index < 3rd percentile) than in less wasted infants (ponderal index > 10th percentile) during the first 3 months after birth. As it is not known how this type of intrauterine malnutrition (I.U.M.) affects growth in early childhood, a group of disproportionally grown S.G.A. infants was followed-up from birth till the age of 3 years.

Material and Methods

25 Consecutively born S.G.A. infants (birthweight below the 10th percentile for gestational age of the Kloosterman curves (11)) who showed clinically evident wasting, had a ponderal index below the 5th percentile of Miller and Hassanein (1) and were free from fetal diseases (congenital infections, congenital anomalies, and chromosomal aberrations), where prospectively studied. 25 Healthy normally grown infants (birthweight between the 10th and the 90th percentiles for gestational age (11) and ponderal index well aboven the 10th percentile (1)) acted as controls. All infants were Caucasian singletons born at a gestational age between 38 and 42 weeks, as verified by the Dubowitz score (12).

The two groups were carefully matched for place of delivery, duration of admission to the hospital, feeding practice when leaving the wards (breast feeding or formula feeding), gesta-

tional age, sex (each group consisted of 12 girls and 13 boys), birth rank, social class and age at follow-up. The infants were drawn from 2 previous studies in which we established highly significant correlations between ponderal index and skinfold thickness (8) and between ponderal index and skeletal retardation (13). Using methods previously described (8,13) weight, length, head circumference, and skinfold thickness were measured after birth. At the age of 3 months (± 1 week), 6 months (± 1 week), 9 months (± 1 week), 12 months (± 2 weeks), 18 months (± 2 weeks), 24 months (± 2 weeks) and 30 months (± 2 weeks) weight and length measurements were repeated. At a mean age of 38 (±3) months (range 31-42 months) head circumference, triceps and subscapular skinfolds were estimated in combination with measurements of weight and length. Skinfolds were measured with a Holtain caliper and the techniques described by Tanner and Whitehouse (14).

For both groups means and standard deviations of weight, length, and ponderal index values were calculated at all indicated points of time. By means of a two-stage Bayesian model (15) mean growth velocity curves were constructed using all available weight, length, and (calculated) ponderal index values. These curves were converted into curves expressing the difference in weight (in kg/month), length (in cm/month) and ponderal index growth velocities between both groups (I.U.M. group minus controls) and their 95% confidence bands. Using the head circumference values obtained at birth and at re-assessment the mean head circumference growth in cm per month over the period was calculated for each group. The skinfold measurements at three year of age were compared with the standard values for British children provided by Tanner and Whitehouse (14). In all instances means and standard deviations with p values were determined by unpaired two-tailed t-tests.

Results

Table 1 provides data about the clinical course of the pregnancies concerned, table 2 presents the mean values for gestational age, weight, length, head circumference, ponderal index, and abdominal skinfold thickness at birth in both groups of infants as well as the mean (measured) height of their parents (the parents were not weighed, so their ponderal index could not

Table 1 Data on the clinical course of the pregnancies

Parameter	I.U.M. infants $n=25$	Controls $n=25$
Primigravidae	17	17
Toxemia	14	2
Smoking	12	11
IUGR >36 weeks of gestation	21	0
IUGR not diagnosed	4	0
Artificial delivery	0	0

Table 2 Mean values of growth parameters at birth

Parameter	I.U.M. infants (SD)	Controls (SD)	P
Gestational age, weeks	39.5 (1.3)	39.7 (1.2)	NS
Weight, kg	2.37 (0.23)	3.43 (0.40)	<0.001
Length, cm	48.3 (1.5)	50.8 (1.8)	<0.001
Head circumference, cm	33.1 (1.3)	34.5 (1.0)	<0.001
Ponderal index	2.13 (0.10)	2.61 (0.15)	<0.001
Abdom. skinfold, mm	2.3 (0.4)	3.7 (0.6)	<0.001
Height mothers, cm	163 (6.2)	165 (8.7)	NS
Height fathers, cm	173 (7.5)	175 (9.3)	NS

be calculated). Though the I.U.M. infants are clearly underweight-for-length, their mean length and head circumference values are also smaller in comparison with the controls. Till 6 months of age the I.U.M. infants show a significant greater weight growth velocity than the controls (fig. 1). Despite the above average rate of weight growth the mean weight growth curve of the I.U.M. group remains permanently below the 10th percentile of the national weight growth curve (16) (fig. 2). 13 Out of 25 I.U.M. infants and 2 out of 25 controls had a weight below the national 10th percentile at the age of 3 years.

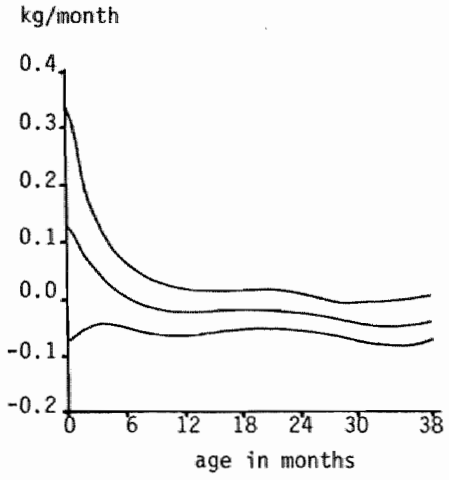

Fig. 1 Difference in mean weight growth velocities. The centre line expresses the difference in weight growth velocity (I.U.M. group minus controls) for chronological age, expressed as kg/month. The exterior lines constitute the 95% confidence bands.

The length growth velocity of the I.U.M. group is slightly greater during the first 12 months after birth than that of the controls (fig. 3). At 12 months of age the group of I.U.M. infants crosses the 10th percentile of the national length growth curve (16), (fig. 4). Ultimately 9 out of 25 I.U.M. infants and 3 out of 25 controls remained below the national 10th percentile.

In comparison with the controls the mean ponderal index curve of the I.U.M. group rises quickly after birth due to the initially greater weight growth velocity (fig. 5). From 9 till 18 months the mean ponderal index of both groups are comparable, whereafter the mean ponderal index of the I.U.M. group lags behind as their weight gain is overshadowed by their gain in length. At the age of 3 years the I.U.M. group is still underweight for length (table 3), but the differences in length and head circumference between I.U.M. infants and controls have grown much smaller than

at birth. The mean head circumference growth velocity over the 3-year period amounted to 0.43 cm/month for the I.U.M. group and 0.41 cm/month for the controls, but the difference is not statistically significant. 4 out of 25 I.U.M. infants had a head circumference below the 5th percentile of Nellhaus (17) versus none of the controls at the age of 3 years.

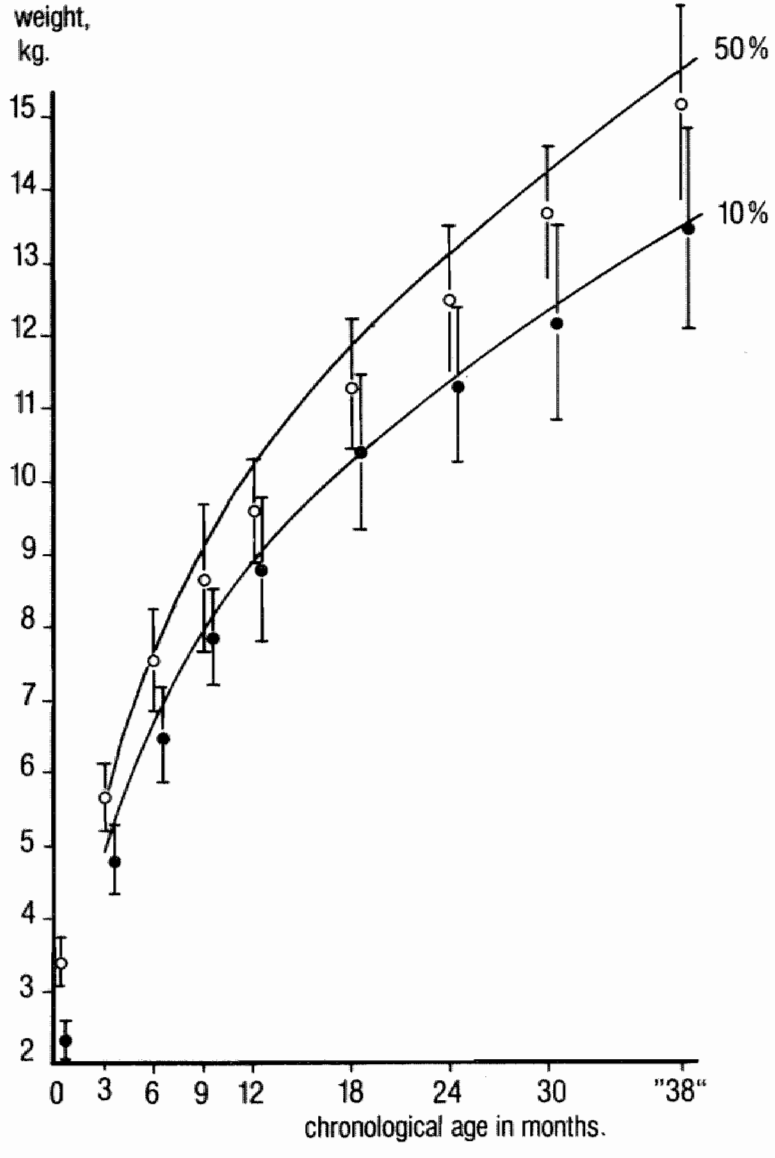

Fig. 2 Mean weight growth curves, in comparison with national standards (16). o, controls; ●, I.U.M. infants.

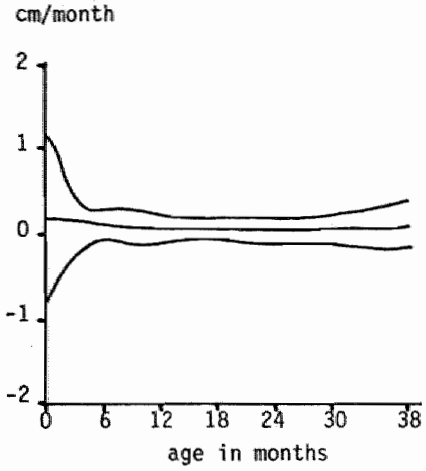

Fig. 3 Difference in mean length growth velocities. The centre line expresses the difference in length growth velocity (I.U.M. group minus controls) for chronological age, expressed as cm/month. The exterior lines constitute the 95% confidence bands.

At the age of 3 years the mean triceps and subscapular skinfolds of the controls compare well with the 50th percentiles for British children of Tanner and Whitehouse (14), while the skinfolds of the I.U.M. infants remain well below these standards. The differences between the 2 groups are highly significant ($p < 0.001$, table 3) and resemble the situation at birth (table 2).

Table 3 Mean values of parameters at 3 years of age

Parameters	I.U.M. infants (SD)	Controls (SD)	*P*
Age, months	37.9 (3.4)	37.9 (3.4)	NS
Weight, kg	13.5 (1.4)	15.2 (1.3)	<0.001
Length, cm	95.3 (3.7)	97.3 (4.0)	<0.05
Head circumference, cm	49.1 (1.8)	50.2 (1.0)	<0.05
Ponderal index	1.56 (0.14)	1.65 (0.14)	<0.05
Triceps skinfold, mm	9.6 (1.1)	11.1 (1.3)	<0.001
Subscapular skinfold, mm	5.9 (0.6)	6.7 (0.5)	<0.001

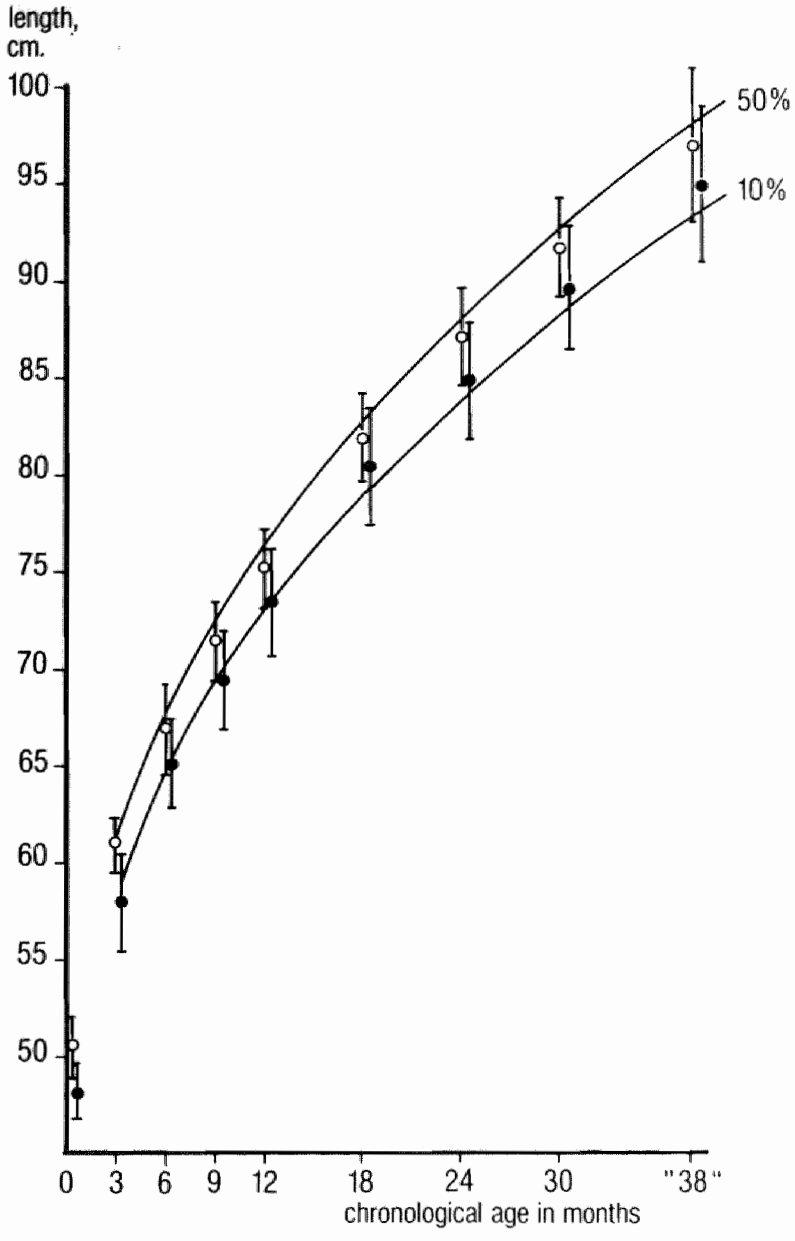

Fig. 4 Mean length growth curves, in comparison with national standards (16). o, controls; ●, I.U.M. infants.

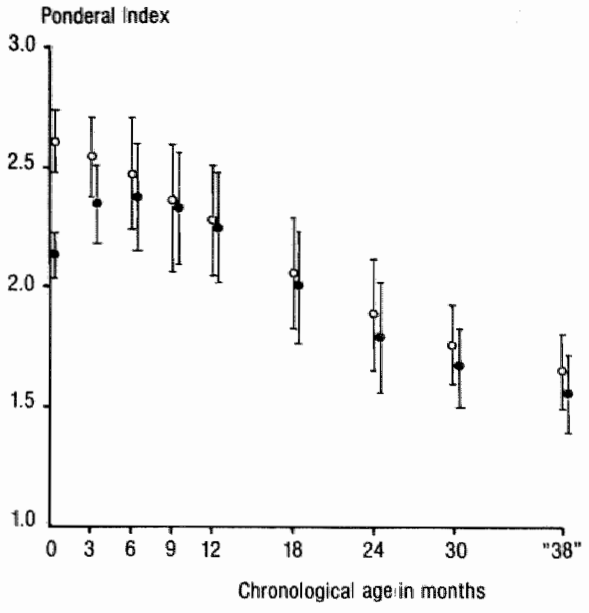

Fig. 5 Mean ponderal index values from 0 till 3 years of age. o, controls; ●, I.U.M. infants.

Discussion

Despite the presence of postnatal catch-up growth the infants who showed disproportionate intrauterine growth retardation at birth (the I.U.M. group) continued to be underweight-for-length and lean at the age of 3 years. The upward shift in length and head circumference is greater than that for weight. However, when disproportionally grown infants are considered individually there is still a considerable diversity in growth profiles, a situation common within populations of S.G.A. infants (18).

Though a subgroup of S.G.A. infants was studied, the results of this study compare well with those of authors (18-22) who followed-up S.G.A. infants defined by birthweight for gestational age only and who established that S.G.A. infants are lighter, smaller and have a smaller head circumference at pre-school age. Chamberlain et al. (20,21) remarked that S.G.A. infants were

relatively underweight-for-length at 22 and 42 months of age but did not quantify this by using a weight-length ratio, like e.g. the ponderal index.

Davies et al. (10) showed that in the first 3 months after birth disproportionally grown term S.G.A. infants (with a ponderal index below the 3rd percentile) gain more rapidly in weight, length and head circumference than more proportionally grown term S.G.A. infants (with a ponderal index between the 10th and 50th percentiles) whereas in both groups rates of growth in each of the 3 months after birth were greater than in normal term infants.

This study partially confirms the findings of Davies et al. (10), but also shows that the catch-up growth in disproportionate intrauterine growth retardation is not complete at the age of 3 years. In fact disproportionate intrauterine growth retardation leads to a growth pattern resembling that of the whole group of S.G.A. infants in early childhood. Possibly this is due to the presence of many disproportionally grown infants in the groups of S.G.A. infants studied. A most interesting finding is the development of the ponderal index in the two groups. At birth the difference is large, at 12 months of age the difference is very small, but at the age of 3 years the difference is again statistically significant. The change from birth till the age of 12 months has also been reported by Davies and Beverly (23), but the picture at 2-3 years of age is an unknown feature. Nutritional habits of both groups did not differ widely and eating problems were equally common (24). Though matching of social class was done at birth, the distribution of the social class hardly changed in the ensuing years. However, the I.U.M. infants turned out to be more often hyperactive than the controls at the age of 3 (24,25) and this may be the reason why their mean weight gain was retarded resulting in a low ponderal index.

Gruenwald (2) supposed that intrauterine growth retardation in the later weeks of pregnancy (i.e. disproportionate growth) would result in complete catch-up growth after birth. This study denies this postulation and provides evidence that even intrauterine growth retardation of short duration may have longterm adverse effects upon later physical growth. Further follow-up studies are necessary to establish the ultimate growth potential of infants affected by disproportionate growth retardation.

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PUBLICATION V: SKELETAL MATURITY AT BIRTH AND AT THE AGE OF 3 YEARS OF INFANTS MALNOURISHED IN UTERO

Summary

Twenty-five term infants malnourished in utero and 25 matched controls were studied at birth and at 2½-3½ years of age. At birth the infants malnourished in utero had a significant retardation in skeletal maturity in comparison with the control group. At 2½-3½ years of age the average skeletal maturity of the intrauterine malnourished children approached that of the controls. However, those with a length below the national 10th centile still showed a retarded skeletal growth in comparison with those who had reached a length above the 10th centile for age.

Introduction

One of the characteristics of infants malnourished in utero (I.U.M.) is the fact that their skeletal maturity at birth is retarded (6). Using the ponderal index as a measure of the nutritional state of these infants at birth, Roord et al. (4) established a close relation between ponderal index ($100 \times W/L^3$) and skeletal maturity at birth.

The ultimate catch-up of skeletal maturity in I.U.M. infants is unknown in the long term, however. As part of a prospective study we investigated 25 I.U.M. infants and 25 controls, matched for age, sex, birth rank and social class, at the age of 2½-3½ years (average 3 years and 2 months) in order to see whether the retarded skeletal maturity diagnosed at birth among the I.U.M. group caught up during the first years of life.

Methods

Thirty one term I.U.M. infants (4) were studied at birth in comparison with 25 normally grown term infants, admitted to the neonatal ward. All were Caucasian singletons born at a gestational age between 38 and 42 weeks, verified by the Dubowitz score. Intrauterine malnutrition was defined as: (1) clinically evident wasting; (2) ponderal index (100 x W/L^3) on or below the 10th centile of Lubchenco et al. (3); and (3) absence of signs of congenital malformation, congenital infection and chromosomal malformation. Weight and length were recorded at birth and the ponderal index calculated. Skeletal maturity was determined within 2 days after birth by means of an anterior-posterior X-ray film of the knee and a lateral film of the foot (4). The maturity standards of Russell (5) based on amenorrhoea in weeks were used.

At 2½-3½ years of age 25 of the 31 I.U.M. children (4 had moved to other regions, 2 families did not assent to re-investigation) were extensively assessed for growth, behaviour, neurology and language development. As the original 25 controls were all born after artificial deliveries, it was necessary to define a new group of 25 controls from healthy attenders of local child health clinics without perinatal problems or chronic diseases. These new controls were matched for age, sex, birth rank and social class. Weight and height were measured in all children and the ponderal index calculated. By means of an anterior-posterior X-ray of the left hand and wrist skeletal maturity in months of age was established using the TW2 rating system described by Tanner and Whitehouse (8).

Results

Mean values and standard deviations for weight, length, ponderal index and skeletal maturity at birth are presented in table 1.

Table 1 Mean growth parameters at birth

Parameter	Controls (S.D.)	I.U.M. infants [1] (S.D.)	P-value
Weight (g)	3433 (398)	2372 (229)	<0.001
Length (cm)	50.8 (1.8)	48.3 (1.5)	<0.001
Ponderal index	2.61 (0.15)	2.13 (0.10)	<0.001
Skeletal maturity [2]	39.1 (1.0)	36.7 (1.3)	<0.001

[1] Figures of the 25 I.U.M. infants re-investigated at $2\frac{1}{2}$—$3\frac{1}{2}$ years of age.
[2] Expressed as amenorrhoea in weeks, mean amenorrhoea of controls was 39.7 weeks and of I.U.M. infants 39.5 weeks.

Table 2 Mean growth parameters at 2½-3½ years (average 37.9 months) of age

Parameter	Controls (S.D.)	I.U.M. infants (S.D.)	P-value
Weight (kg)	15.2 (1.3)	13.5 (1.4)	<0.001
Length (cm)	97.3 (4.0)	95.3 (3.7)	N.S.
Ponderal index	1.65 (0.14)	1.56 (0.14)	<0.05
Skeletal maturity [1]	37.1 (4.3)	36.2 (5.4)	N.S.

[1] Expressed as bone 'age' in months of age.
N.S., not significant.

The figures obtained at 2½-3½ years of age are shown in table 2. Statistical analysis was done by using paired t-tests.

Figures 1 and 2 show the actual measurements of skeletal maturity at birth in relation to gestational age and at 2½-3½ years of age in relation to age in months, respectively.

Tables 1 and 2, as well as figures 1 and 2 clearly show that at the age of 3 years the significant differences in skeletal maturity between the I.U.M. children and normal controls, established at birth, have disappeared. Though the mean ponderal index values at birth and at 3 years of age are lower in the I.U.M. group, no correlation between ponderal index and skeletal maturity at follow-up could be established despite the firm relation between these two at birth ($r = 0.67$, $p < 0.001$) (4). Nine children of the I.U.M. group had a length at follow-up below the national 10th centile for age (9). Their mean age was 39.7 months, but their mean skeletal maturity only 34.4 months. The 16

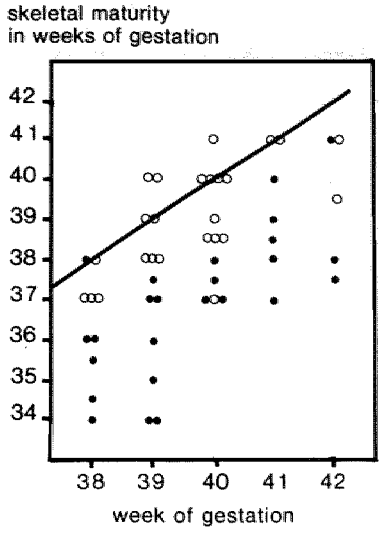

Figure 1 Skeletal maturity at birth in relation with gestational age. o, controls; ●, I.U.M. infants.

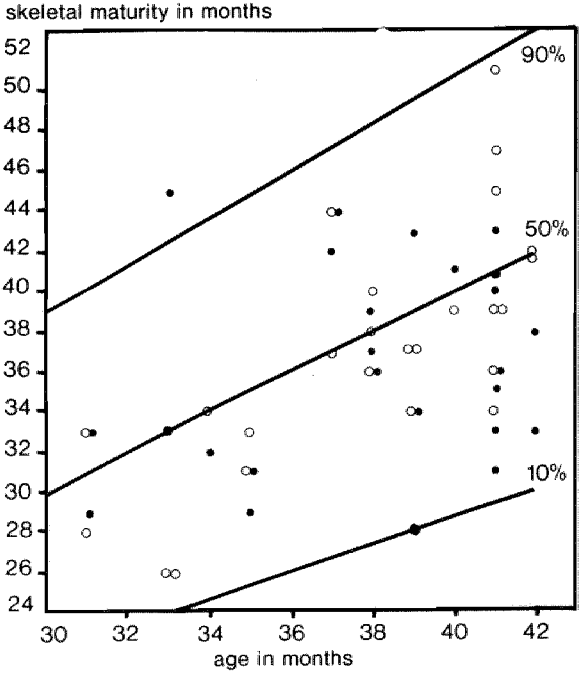

Figure 2 Skeletal maturity at 2½-3½ years of age (average 3 years and 2 months) in relation with chronological age. o, controls; ●, I.U.M. infants.

I.U.M. children with a length above the 10th centile for age had a mean age of 36.9 months and a mean skeletal maturity of 37.2 months. This difference of 5 months was statistically significant ($p < 0.025$).

Discussion

At birth the duration and severity of the adverse fetal environment is reflected by the degree of skeletal growth retardation (4). In the ensuing months and years physical recovery takes place. In this study children previously malnourished in utero show lower mean values for weight, length and ponderal index at the age of 3 years in comparison with matched controls, but the differences are becoming smaller than at birth. This same finding applies to skeletal maturity. Only those with a length below the national 10th centile of length for age show retarded skeletal growth, which implies a relation between length and skeletal maturity. This fact was also reported by Fitzhardinge and Steven (1) studying S.G.A. children after the age of 4 years. They used the Greulich-Pyle atlas (2) for the estimation of skeletal maturity which represents more rapidly maturing children than that of Tanner and Whitehouse (8).

Tanner et al. (7) showed a high correlation between height at 3 years of age and adult height, which would imply that about one third of the intrauterine malnourished children will grow up into relatively small adults. This is difficult to understand as these children mostly have a retarded skeletal maturity at 3 years of age, which might be a sign that they have a greater potential for prolonged linear growth.

Further study of these children is necessary. Also it will be necessary to determine the time when, between 0 and 3 years of age, I.U.M. children start to catch-up in skeletal maturity. A study by our group is being conducted to answer this question.

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PUBLICATION VI: DEVELOPMENTAL ASPECTS OF SUBACUTE FETAL DISTRESS: BEHAVIOUR PROBLEMS AND NEUROLOGICAL DYSFUNCTION

Summary

A group of term infants malnourished in utero and classified as subacute fetal distress at birth were followed up with a group of normally grown term infants matched for age, sex, birth rank and social class. Both groups were free from other perinatal morbidity and chronic diseases. At three years of age behaviour was studied using the behaviour screening questionnaire of Richman and Graham and a behaviour observation report, whereas neurological dysfunction was assessed according to the proforma of Touwen. Both problematic behaviour and neurological dysfunction occurred more frequently in the subacute fetal distress group. Behaviour problems are comparable to neurological signs as indicators for brain dysfunction.

Introduction

Gruenwald (6) first called attention to the fact that the weight of most organs of small-for-gestational age (S.G.A.) infants are reduced. While the liver, spleen, adrenals and thymus are severely reduced in size, brain and pancreas appear to be the least affected. The human brain initiates the period of rapid weight gain during the last half of fetal life, with a peak near the time of birth which then decreases over the first year of postnatal life (3).

There are two major periods of brain cell multiplication: one (the neuroblasts), from 15 to 20 weeks of gestation and one (the glia) which commences at about 25 weeks of gestation. This second

period probable ends in the second year after birth (2). Approximately two-thirds of the human brain cells, as represented by DNA, accumulate prior to birth (20). The 'brain growth spurt' may be a period of enhanced vulnerability to nutritional restriction (3). Timing in relation to birth, severity and duration of intrauterine growth retardation will determine the final growth limitation of the brain. In guinea pigs (who, like humans, initiate the brain growth spurt in utero) adequate postnatal nutrition offsets some, though not all of the biochemical changes resulting from intrauterine growth retardation (1). Thomas et al. (16) demonstrated by means of stereological analysis of the brains of rats undernourished from birth (within the brain growth spurt) a deficit in the synapse to neuron ratio. The question arises whether the brain changes produced by intrauterine growth retardation are functionally important and reversible during the period of nutritional rehabilitation after birth. At school age problematic behaviour is more frequently encountered in S.G.A. infants than amongst infants without perinatal morbidity (10). Richman et al. (13) showed that the rate of behaviour problems at three years of age is very similar to that in later childhood and early adolescence. Early detection of behaviour problems is therefore possible but well-defined criteria have to be used as most behaviour problems at preschool age consist of exaggeration or inappropriate prolongation of normal behaviour patterns. The behaviour screening questionnaire (BSQ) developed by Richman and Graham (12) is a valid screening tool in this field (13), especially if substantiated by observation of the child's behaviour. Behaviour is a complex function of the nervous system, dysfunction of this system can be further substantiated by neurological assessment. A proper tool therefore is the examination proforma for minor neurological dysfunction of Touwen (17). This consists of an observation of the child's motor behaviour and the

testing of specific nervous functions.

Using behaviour and neurological examination as parameters we assessed at the age of 3 years the outcome of a group of term infants who were malnourished in utero and were classified as subacute fetal distress due to their disproportional growth at birth. According to Gruenwald (7) the growth retardation in these infants started a few weeks before birth, they appeared wasted at birth due to loss of subcutaneous adipose tissue and loose skinfolds (14). In earlier studies we reported about their physical growth (18,19).

Subjects and Methods

25 Term infants showing disproportional growth and a subnormal nutritional state at birth (subacute fetal distress) were prospectively studied in comparison with 25 normally grown term infants of both sexes and from all social classes. All were Caucasian singletons born at a gestational age of between 38 and 42 weeks, as verified by the Dubowitz score (4).

The study group was drawn from 2 previous studies in which we established highly significant correlations between ponderal index (weight in grams x 100/length^3 in cm's) and skinfold thickness (14) as well as skeletal retardation (15). Selected were those infants who: 1) showed clinically evident wasting, 2) had a ponderal index on or below the 10th centile of Lubchenco et al. (9), 3) were free from fetal diseases (congenital infections and anomalies, chromosomal aberrations) and 4) did not have further perinatal complications(such as artificial delivery, asphyxia, hypothermia, hyperbilirubinemia, hypoglycaemia and hyperviscosity). All had a birthweight on or below the 10th centile of the Kloosterman curves (8).

The control group consisted of infants with a ponderal index above the 25th centile (9), a birthweight well above the 10th

centile (8) and an uneventful perinatal period. The two groups were matched for age, sex, birth rank and social class. All children were free from chronic and/or debilitating diseases from birth onwards. In none of the families severe relational or parental problems were present and all families were representative for their social class.

At a mean age of 3 years and 2 months (range 31-42 months) behaviour and neurology were assessed. The behaviour screening questionnaire (BSQ) was completed by the first author in a short interview with the mother (sometimes accompanied by the father). The 12 items of the behaviour scale were taken from the 60 questions dealing with the current health, development and behaviour of the child as described by Richman and Graham (12). The items of problem behaviour concerned: 1) eating, 2) sleeping, 3) soiling, 4) activity, 5) concentration, 6) relations witn other children, 7) attention seeking and dependency, 8) difficulty to manage, 9) tempers, 10) mood, 11) worries and 12) fears. A 3-point rating scale was used: a score of 0 indicates that the problem behaviour is absent, a score of 1 that it is sometimes present or present to a mild degree and a score of 2 that it occurs frequently or to a marked degree. Activity could only be scored as 0 (normal) and 2 (hyperactive). The score of each child was summed, a score of 10 or more points interpreted as showing moderate to severe behaviour problems (13). All items were also analysed seperately.

As parental reports on specific items of behaviour might be inaccurate all children were also clinically assessed in the presence of the parent(s) by a second examiner (T.K.) to avoid bias. A behaviour observation report (BOR) was used, consisting of 8 items: 1) activity, 2) concentration, 3) attention seeking and dependency, 4) negativism, 5) insistency, 6) destructivity and aggression, 7) fidgetiness and 8) fears. These items were

formulated according to the lines used in the BSQ and again a 3-point score was used. A summed score of 7 or more (using the same 40% cut-off point as in the BSQ) was interpreted as the presence of moderate to severe behaviour problems during observation.

Neurological dysfunction was studied using the 26 items suitable for children of 3 years of age of the examination proforma for minor neurological dysfunction of Touwen (17). A score of 0 meant an optimal and a score of 1 a suboptimal performance for chronological age of the item by the individual child. The items tested are presented in table 4. Summed scores were calculated and all items were also analysed separately.

The study was carried out blindly, none of the examiners knew the history or former examination results of the children. Statistical analyses were performed by means of the X^2-test.

Results

To provide a picture of the children in this study, some perinatal figures are presented in table 1 (see also reference 19).

Using the summed BSQ scores the differences between the two groups just failed to reach statistical significance ($X^2 = 3.323$, DF = 4). The controls had a mean summed BSQ score of 6.1 (s.d. 3.6) and the subacute fetal distress group of 7.6 (s.d. 4.1).

Table 1 Mean parameters at birth of the subacute fetal distress group and the controls (see ref. 19)

	Subacute fetal distress group (S.D.)	Controls (S.D.)	P
Birthweight (kg)	2.37 (0.23)	3.43 (0.40)	<0.001
Ponderal index	2.13 (0.10)	2.61 (0.15)	<0.001
Gestational age (wks)	39.5 (1.3)	39.7 (1.2)	n.s.
Present age (mths)	37.9 (3.4)	37.9 (3.4)	n.s.

n.s., not significant.

Table 2 Cell frequency counts of controls and subacute fetal distress children in the behaviour screening questionnaire (BSQ)

Items BSQ	Subacute fetal distress group ($n=25$)			Controls ($n=25$)			Statistics		
	score=0	score=1	score=2	score=0	score=1	score=2	χ^2	DF	P
Eating	18	4	3	14	9	2	2.676	2	n.s.
Sleeping	20	3	2	19	1	5	2.400	2	n.s.
Soiling	18	0	7	23	0	2	3.553	1	<0.03
Activity	7	0	18	13	0	12	3.036	1	<0.04
Concentration	8	4	13	10	9	6	4.837	2	<0.05
Relations	17	1	7	19	0	6	1.574	2	n.s.
Attention seeking/dependency	19	1	5	14	4	7	3.023	2	n.s.
Difficulty to manage	12	4	9	10	6	9	0.585	2	n.s.
Tempers	11	4	10	12	7	6	1.883	2	n.s.
Mood	23	1	1	22	3	0	2.455	2	n.s.
Worries	21	2	2	24	0	1	3.313	2	n.s.
Fears	15	8	2	24	0	1	13.526	2	<0.0006
Total	189	32	79	204	39	57	4.821	2	<0.05

Table 3 Cell frequency counts of controls and subacute fetal distress children in the behaviour observation report (BOR)

Items BOR	Subacute fetal distress group ($n=25$)			Controls ($n=25$)			Statistics		
	score=0	score=1	score=2	score=0	score=1	score=2	χ^2	DF	P
Activity	7	1	17	13	5	7	9.036	2	<0.006
Concentration	9	2	14	15	5	5	7.283	2	<0.01
Attention seeking/dependency	17	1	7	17	3	5	1.381	2	n.s.
Negativism	16	3	6	19	2	4	0.862	2	n.s.
Insistency	19	0	6	21	0	4	0.125	1	n.s.
Destructivity/aggression	20	0	5	22	0	3	0.149	1	n.s.
Fidgetiness	21	0	4	23	0	2	0.189	1	n.s.
Fears	13	3	9	24	0	1	14.840	2	<0.0003
Total	122	10	68	154	15	31	18.538	2	<0.0002

However, 4 of the 12 items of the BSQ were more frequently encountered in the group of subacute fetal distress children. These were soiling, hyperactivity, concentration disorders and fears (table 2).

The summed BOR scores showed that behaviour problems were significantly more common in the subacute fetal distress group (mean score 5.8 and s.d. 3.2) than in the controls (mean score 3.1 and s.d. 2.6), (X^2 = 11.800, DF = 5, $p < 0.02$). Table 3 demonstrates that in this assessment also hyperactivity, concentration disorders and fears occurred more often in the subacute

fetal distress group. A firm interrelationship could be established between the summed BSQ and BOR scores (X^2 = 18.706, DF = 6, $p < 0.005$).

Table 4 Cell frequency counts of controls and subacute fetal distress children in the neurological assessment

Neurological items according to subsystems *	Subacute fetal distress group (n=25)		Controls (n=25)		Statistics		
	score=0	score=1	score=0	score=1	X^2	DF	P
(1) Sensorimotor apparatus:							
Muscle power	25	0	25	0	0.000	1	n.s.
Resistance to passive movement	24	1	25	0	1.020	1	n.s.
Range of movements	22	3	25	0	3.191	1	<0.04
Tendon reflexes	23	2	25	0	2.083	1	n.s.
Plantar response	19	6	22	3	1.219	1	n.s.
Skin reflexes	24	1	25	0	1.020	1	n.s.
(2) Posture:							
Standing, general	14	11	21	4	4.667	1	<0.02
Extended arms, standing	18	7	20	5	0.438	1	n.s.
Walking	19	6	19	6	0.000	1	n.s.
Gait	14	11	20	5	3.309	1	<0.04
Inspection of the back/spine	23	2	24	1	0.355	1	n.s.
Lying in prone/supine position	23	2	24	1	0.355	1	n.s.
(3) Gross motor functions:							
Walking on tiptoe	24	1	24	1	0.000	1	n.s.
Walking on heels	18	7	21	4	1.049	1	n.s.
Standing on one leg	23	2	25	0	2.083	1	n.s.
Hopping on one leg	25	0	25	0	0.000	1	n.s.
(4) Coordination of the extremities:							
Kicking against examiner's hand	24	1	25	0	1.020	1	n.s.
Fingertip touching test	21	4	25	0	4.348	1	<0.02
Standing with eyes closed	18	7	22	3	2.000	1	n.s.
(5) Quality of motility:							
Sitting } speed, smoothness, adequacy of	14	11	23	2	8.420	1	<0.002
Standing } small and gross motor movements	16	9	21	4	2.599	1	n.s.
(6) (Dys)kinesia:							
Chlorciform movements	20	5	25	0	5.555	1	<0.01
Athetotic movements	24	1	25	0	1.020	1	n.s.
(7) Visual system:							
Position and eye movements	25	0	25	0	0.000	1	n.s.
Visual acuity and visual fields	24	1	25	0	1.020	1	n.s
9 Hearing:							
Low voice, localisation of sound	25	0	25	0	0.000	1	n.s.
Total	549	101	611	39	30.771	1	<0.0001

* Adapted from Touwen [17].

At the neurological examination no major neurological defects like cerebral and epilepsia were diagnosed (table 4). The controls presented a mean score of 1.6 (s.d. 1.5) and the subacute fetal distress group of 4.0 (s.d. 2.1). This difference was statistically significant (X^2 = 21.765, DF = 9, $p < 0.005$). 6 Of the 26 neurological items showed significant differences to the detriment of the subacute fetal distress group: range of move-

ments, standing posture, gait, fingertip touching test, quality of motility sitting, and choreiform movements. Hearing and vision (one child used spectacles) were never appreciably affected.

Problematic behaviour and neurological dysfunction turned out to be firmly interrelated. The summed neurological scores correlated well with the summed BSQ scores ($X^2 = 9.040$, DF = 2, $p < 0.025$) and the summed BOR scores ($X^2 = 12.430$, DF = 3, $p < 0.01$).

Table 5 Incidence of problematic behaviour and neurological dysfunctions in both groups

	Problematic behaviour		Neurological dysfunction
	BSQ	BOR	
Subacute fetal distress group	8/25	8/25	9/25
Controls	4/25	2/25	1/25
Total	12/50	10/50	10/50

Individual scores are presented in table 5, the cut-off point of the BSQ score was 10 or more points, of the BOR score 7 or more points and of the neurological score 5 or more (the mean score of the control group plus 2 standard deviations). 2 Children of the control group scored high in the BSQ (both scores = 10), whereas their behaviour during the observation turned out to be normal (BOR scores of both children = 5).

Discussion

The behaviour screening questionnaire (BSQ) is able to select out 100% children with moderate to severe behaviour problems but only just over a third of those with mild behaviour problems (13). Richman et al. (13) reported that using a cut-off score of 10 points on the BSQ there are about 6% false positives (i.e., children assigned to the group of problematic behaviour who on clinical assessment have no or a dubious behaviour problem) and about 10% false negatives (i.e., children in the group of normal

behaviour who on clinical assessment appear to have a mild behaviour problem).

A combination of BSQ with clinical observation (BOR) is therefore more valuable than the BSQ alone. In this way 2 out of 25 controls were found to have a moderate to severe behaviour problem, an incidence comparable to the figure of approximately 7% of a sample of 705 children living in a London borough obtained by Richman and co-workers (13). The incidence of problematic behaviour among the subacute fetal distress infants (8 out of 25) is therefore really high. Our findings compare well with those of Neligan et al. (10) for term controls and S.G.A. infants at 5-7 years of age, in spite of the fact that subacute fetal distress accounts only for a (probably large) subgroup of the S.G.A. population. Hyperactivity and concentration disorders on one side and exaggerated fears on the other side are two characteristic patterns of behaviour of these children which emerged from our study.

The overall neurological picture is clearly different among both groups and as none of the children had significant vision and hearing disorders, the 9 (out of 25) subacute fetal distress infants and the 1 (out of 25) child of the control group can be realistically be classified as showing neurological dysfunction. Fitzhardinge and Steven (5), studying term S.G.A. infants at 4-6 years of age, established a low incidence of major neurological defects (and then especially among those who had sustained severe neonatal asphyxia) and a high incidence (about 25%) of 'minimal brain dysfunction'. Almost the same picture emerges from the study of Neligan et al. (10) among term S.G.a. infants at the age of 5-7 years. Though we assessed a subgroup of S.G.A. infants (subacute fetal distress) at a younger age with a different investigation scheme, our results are comparable with these two studies (5,10).

As both neurological dysfunction and behaviour problems reflect a brain dysfunction, it is not amazing to find the interrelationship between these assessments. The cause of the brain dysfunction in the subacute fetal distress infants is most probably related to the intrauterine malnutrition which they experienced as this was the only variable parameter between the two groups in the study which were also carefully matched to rule out environmental factors as good as possible.

Prechtl (11), realizing that brain lesions are not static and that brain development depends on innate capacities and personal/environmental experience, suggests that if the brain becomes damaged rewiring may occur to a considerable degree. This hypothesis may explain why only one-third of the children in the subacute fetal distress group showed behaviour problems and/or neurological dysfunction.

Concluding, this study shows that despite the relatively short duration of intrauterine malnutrition, subacute fetal distress often results in signs of brain dysfunction at the age of 3 years. Behaviour problems are comparable to neurological signs as indicators for brain dysfunction.

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PUBLICATION VII: LANGUAGE DEVELOPMENT AT THE AGE OF 3 YEARS OF INFANTS MALNOURISHED IN UTERO

Summary

To evaluate if language testing might provide useful information about the developmental outcome at pre-school age of term infants malnourished in utero, a group of these infants was studied in combination with a group of normally grown term infants matched for age, sex, birth rank and social class. Both groups were free from significant neonatal morbidity and debilitating diseases. Intrauterine malnutrition was defined as underweight for gestational age and the presence of wasting to select those S.G.A. infants with recognizable signs of malnutrition at birth. The Reynell Developmental Language Scales were used to test language and the results were related to a separate assessment of behaviour and neurology.

Both verbal comprehension and expressive language were significantly less developed in infants malnourished in utero. A firm relation was established between language delay and behaviour problems. It was concluded that language development can be used to assess the developmental progress of infants malnourished in utero if performed in combination with behaviour assessment. Many of these infants will benefit by speech therapy during behaviour therapy at pre-school age.

Introduction

Animal and human studies have shown that nutritional restriction during the brain growth spurt leads to definite chemical and morphological changes of the brain (Dobbing et al., 1979; Thomas et al., 1979; Winick, 1969). In humans this vulnerable period

starts during intrauterine life (Dobbing et al., 1979) and so intrauterine malnutrition may result into functional brain damage. This is partially reflected by the high incidence of school failures among small-for-gestational age (S.G.A.) infants (Neligan et al., 1976) despite the fact that their average IQ scores are often in the normal range (Babson et al., 1969; Fitzhardinge et al., 1972).

Language may be one of the many possible expressions of brain dysfunction as a result of nutritional restriction during the brain growth spurt. As language develops quickly over the age range of 2 to 5 years and as it is dependent on the biological maturation of the brain (Rutter et al., 1972), it may be useful as a testable higher cerebral function at pre-school age. Fitzhardinge et al. (1972) reported that S.G.A. infants frequently showed speech problems at the age of 3 to 4 years and had to be referred to a speech therapist.

To evaluate if language testing might provide useful information about their developmental outcome, we studied a group of term infants malnourished in utero and a group of matched normally grown controls at the age of 3 years. The Reynell Developmental Language Scales (Reynell, 1969 a) were used to test language development as these scales have a high sensitivity at 3 years of age. As language achievements may be influenced by behaviour and neurological dysfunction, the results are related to the outcome of a previous study of these same infants' behavioural and neurological development (Walther et al., 1981).

The study group consisted of term infants with a birthweight below the 10th national percentile (Kloosterman, 1970) and with clinically evident wasting due to a reduced quantity of subcutaneous adipose tissue (Roord et al., 1978 a). The degree of wasting at birth was quantified by the use of the ponderal index ($100 \times \text{weight}/\text{length}^3$) according to Miller et al. (1971),

Gruenwald (1974), and Roord et al. (1978 a), who proposed the ponderal index as a measure of the nutritional state at birth. By using these two parameters we selected infants who were underweight-for-gestational age and underweight-for-length. Gruenwald (1974) showed that the intrauterine growth retardation in these infants started only a few weeks before birth due to an insufficient supply line (subacute fetal distress). In our opinion these infants are easily recognizable as presenting intrauterine malnutrition (I.U.M.) at birth.

Subjects and Methods

25 Consecutively born term infants showing intrauterine malnutrition were prospectively studied in comparison with 25 normally grown term infants. All were Caucasian singletons born at a gestational age of between 38 and 42 weeks, as verified by the Dubowitz score (Dubowitz et al., 1970).

The infants participated in two earlier studies in which we established highly significant correlations between ponderal index (weight in grams x 100/length^3 in cm) and skinfold thickness (Roord et al., 1978 a) as well as skeletal retardation (Roord et al., 1978 b). The underweight infants (1) showed clinically evident wasting, (2) had a ponderal index below the 5th percentile of Miller et al. (1971), (3) had a birthweight below the 10th percentile of the Kloosterman grid (Kloosterman, 1970), and (4) were free from fetal diseases (congenital infections and anomalies, chromosomal aberrations) and from significant neonatal morbidity. The control group consisted of healthy non-wasted infants who had a ponderal index and a birthweight well above the 10th percentile and an uneventful perinatal period. The two groups were exactly matched for age, sex (12 girls and 13 boys in each group), birth rank and social class. Hearing and vision were intact in all children, chronic diseases were absent and none of

them was bilingual. In their families severe relational or parental problems were absent.

The children were assessed with the Experimental Edition of the Reynell Developmental Language Scales at a mean age of 3 years and 2 months (range 31-42 months). The R.D.L.S. (Reynell, 1969 a) consists of 3 scales: (1) The Verbal Comprehension Scale A uses toys and requires no speech, some hand function is necessary as the child has to point out non-verbally that he understands the examiner, (2) The Verbal Comprehension Scale B is an adaptation of scale A for handicapped children without speech and hand function, nearly all responses can be performed by eye-pointing, and (3) The Expressive Language Scale which is divided into three sections. The expressive language structure section taps the very earliest stages of pre-language, from the earliest vocalizations to the correct use of complex sentences with subordinate clauses. The expressive language vocabulary section assesses the child's ability to name simple objects, pictures, and actions as well as to describe words (and not so much his knowledge of them). In the expressive language content section the ability to verbalize connected thoughts is investigated: the child has to describe 5 different pictures without leading questions. As none of the children were known to be severely handicapped the verbal comprehension scale A and the expressive language scale could be used. The verbal comprehension scale was carried out first as this requires no speech and provides sufficient relaxation to obtain appropriate responses to the expressive language scale from young children. Two experienced speech therapists performed the tests, the mother was always within reach to put the child at his ease.

The raw scores of the different test items were turned into developmental age scores according to the standardization sample (Reynell, 1969 a). The significance of differences of mean values

was determined by the student paired two-tailed t-test.

Results

In Table I the mean growth parameters at birth are presented to provide a picture of the children admitted to this study. In general the group of infants malnourished in utero (I.U.M.) was more difficult to test than the group of controls. Testing often lasted longer due to marked hyperactivity and poorer concentration abilities of these children. Most children fully completed both language scales, however.

Table I Mean growth parameters at birth

	controls (s. d.)	I. U. M. infants (s. d.)	p
Birthweight, g	3.433 (398)	2.372 (229)	$< 0.001^a$
Length, cm	50.8 (1.8)	48.3 (1.5)	$< 0.001^b$
Head circumference, cm	34.5 (1.0)	33.1 (1.3)	$< 0.001^c$
Ponderal index	2.61 (0.15)	2.13 (0.10)	$< 0.001^d$
Gestational age, weeks	39.7 (1.2)	39.5 (1.3)	N. S.

N. S.: not significant
[a] t = 10.9154, DF 24 [b] t = 7.2043, DF 24 [c] t = 8.4913, DF 24 [d] t = 14.2973, DF 24

Table II Language assessment (R.D.L.S.), mean raw scores and developmental ages in months

	Controls (s. d.) raw score	dev. age	I. U. M. infants (s. d) raw score	dev. age	p
Verbal comprehension	41.0 (6.6)	44.1 (6.6)	37.3 (8.1)	40.2 (7.4)	$< 0.05^a$
Expressive language	35.2 (9.3)	35.9 (8.6)	30.0 (12.2)	31.0 (10.7)	$< 0.025^b$
structure	14.2 (3.2)	29.0 (9.0)	13.6 (3.1)	26.1 (6.9)	N. S.
vocabulary	15.6 (4.3)	42.9 (12.0)	12.2 (7.1)	35.7 (21.3)	$< 0.03^c$
content	5.4 (3.8)	30.0 (17.2)	4.3 (3.5)	24.1 (17.5)	N. S.
Mean age		37.9 (3.4)		37.9 (3.4)	N. S.

[a] t = 2.1620, DF 24 [b] t = 2.4137, DF 24 [c] t = 2.3579, DF 24

The mean raw scores and corresponding mean developmental ages of the language assessment are presented in Table II. The achievements were worse for the I.U.M. children than for the controls. The differences amounted to 4 months for verbal comprehension and 5 months for expressive language and were statistically significant at the 5% level. Girls tended to score higher than boys on both scales (a common phenomenon), but the same differences between both groups were found in either sex.

Table III Relation of language achievement to behaviour problems and neurological dysfunction

Language achievement		Behaviour problems	Neurological dysfunction
Delayed	2 controls	0	0
	8 I. U. M. infants	6	4
Adequate	23 controls	2	1
	17 I. U. M. infants	2	5

[a] see reference 24

Figure 1 shows that many children were more advanced in verbal comprehension in comparison with the standard. Only one child (of the I.U.M. group) had a very low score, i.e. more than 2 standard deviations below the standard mean for chronological age. Many

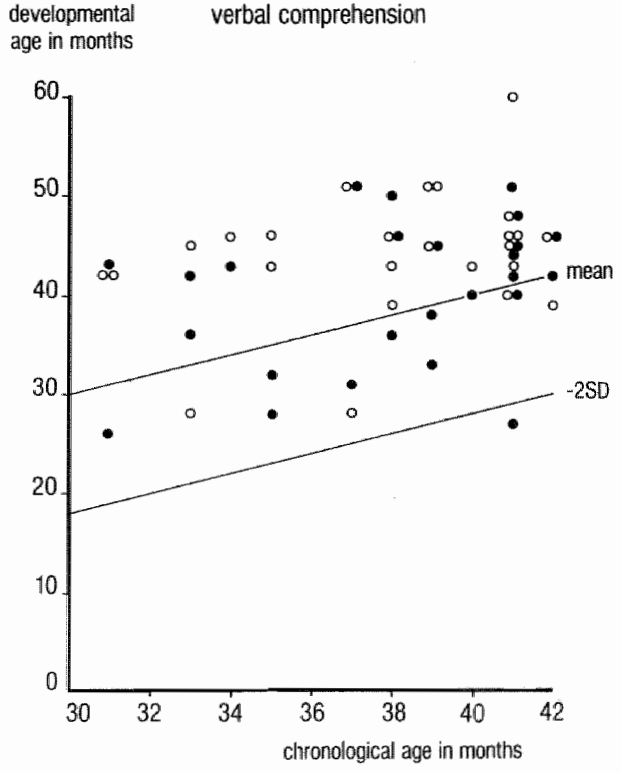

Figure 1 Verbal comprenension, developmental age in months versus chronological age in months; o = controls and ● = I.U.M. infants.

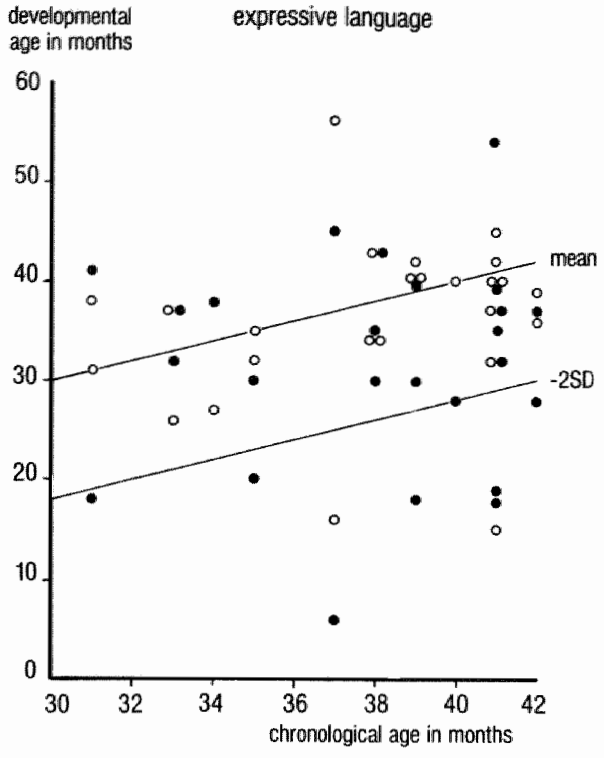

Figure 2 Expressive language, developmental age in months versus chronological age in months; o = controls and • = I.U.M. infants.

more children presented an expressive language delay (figure 2): 2 controls and 8 I.U.M. children scored 2 or more standard deviations below the standard mean. 6 Of these 10 children were of lower ability in verbal comprehension as they scored more than one standard deviation below the mean. Of the three sections of expressive language only the vocabulary scores showed statistically significant differences to the detriment of the I.U.M. group with 1 control and 6 I.U.M. children scoring more than 2 standard deviations below the standard mean. As structure develops quicker than vocabulary and content is the last of the three expressive language sections to develop (Reynell, 1969 a) at the test age, the latter section provides too little information to

be representative. Expressive language structure scores were relatively low in both groups but the mean values were comparable.

Finally 2 (out of 25) controls and 8 (out of 25) I.U.M. children were classified as language retarded on the verbal comprehension and/or expressive language scales (with scores of 2 or more standard deviations below the standard mean). Using the criterion that language delay implies an achievement < 2/3 chronological age, the same children were identified. The incidence of behaviour problems in I.U.M. infants with language delay was high, whereas neurological dysfunction occurred to about the same extent in I.U.M. infants with and without language delay (Table III). The relation of language delay to behaviour problems is statistically highly significant (X^2 = 12.5, DF = 1, $p < 0.0005$).

Discussion

Ideally language assessment procedures measure verbal comprehension, expressive language, articulation, and intelligibility (Randall et al., 1974). The latter performance can only be rated subjectively and does not add much information as most children are easily intelligible at the age of 3 years (Randall et al., 1974), therefore it was omitted in this study.

Initially we tried to investigate articulation by means of the 'Utrecht articulation test' (Peddemors-Boon et al., 1977) for 3-6 year old children. But practice soon learned that the test was too extensive (106 items) and took too much time after the completion of the R.D.L.S. for these young children. As severe articulation defects will affect the structural aspects of expressive language (because the child uses short and incomplete sentences, Reynell, 1969 b), without affecting the vocabulary and content sections, and as articulation difficulties are a poor indicator of the child's true language development at the age of

3 years (Randall et al., 1974), the use of the articulation test was discontinued. The statistically not significant differences in expressive language structure in this study show that severe articulation defects are not more common among the children malnourished in utero.

The higher level of performance on the verbal comprehension scale in comparison with the standardization sample of Reynell has been described before (Randall et al., 1974; Stevenson et al., 1976) and did not influence the identification of language delay.

Due to the absence of agreed criteria for language delay at different ages, the prevalence of the problem is not well known. In pediatric practice the most widely used criterion is referral to a speech therapist (Bax et al., 1980; Fiedler et al., 1971; Schwartz et al., 1975) which leads to widely varying prevalence figures. MacKeith and Rutter (1972) report that at school entrance 1% of the children show a marked language handicap whereas another 4 to 5% present the sequelae of earlier language difficulties. At the age of 3 years the prevalence rate of delayed language development varies from 2.5% (Randall et al., 1974) to 6.8% (Stevenson et al., 1976) and 8.5% (Silva, 1980). The high rate of (especially expressive) language delay among the I.U.M. group in this study (32%) is therefore remarkable.

In a study of the behaviour of 3-year-old children Richman and Graham (1971) experienced that language delay was a common feature in children considered to have behaviour problems, neurological dysfunction or retardation. The same phenomenon emerges in this study. It indicates that language delay can be considered as one of many possible expressions of brain dysfunction as a result of nutritional restriction during the brain growth spurt.

Fitzhardinge and Steven (1972), studying term born S.G.A. infants (defined as having a birthweight below the 3rd percentile

for gestational age) at 3 to 4 years of age, reported that 25% presented signs of minimal brain dysfunction and that 29% had speech problems and were referred to a speech therapist. In their material articulation defects were few, both receptive and expressive abilities were poor and many children had a poor vocabulary. Though we assessed a subgroup of S.G.A. infants (i.e. those S.G.A. infants showing clear-cut signs of intrauterine malnutrition) systematically using the R.D.L.S., our results compare well with those of Fitzhardinge and Steven (1972). As the results of our study are in entire agreement with the data of Fitzhardinge and Steven (1972) despite the different definitions of 'intrauterine malnutrition', it seems justified to suppose that there is a relation between intrauterine malnutrition and delayed language development. As language delay is often seen in I.U.M. infants with significant behaviour problems (like concentration disorders and hyperactivity) these infants may benefit greatly by speech therapy in combination with behaviour therapy.

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