

## **The growth of brain and muscles in premature neonates:**

### **A comparison between antenatal and postnatal periods (Infants from birth to 40 days of life)**

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## Background

The importance of growth during the fetal and postnatal periods needs to be considered for the future, for it concerns the infant's developmental, cardiovascular, immunological, renal and metabolic outcomes.

## Methods

We conducted a longitudinal study in 150 premature neonates on their growth of brain, cerebellum, subcutaneous adipose tissue and skeletal muscles. The intrauterine growth was considered retarded if body weight (BW) and the ponderal index (PI) was below the 10<sup>th</sup> centile according to the Lubchenco's neonatal chart. The population was hence divided in two groups: one having experienced a normal intrauterine growth (NIUG, n = 125, 32.7 ± 2.9 weeks, 1858 ± 574 g) and the other a restricted or retarded intrauterine growth (RIUG, n=25, 33.9 ± 3.95 weeks, 1545 ± 559 g). The considered parameters were the global anthropometry: weight or BW, length or BL, head circumference or HC. The cerebral mass (CM) was calculated from head circumference according to Dobbing. The growth of brain and cerebellum was evaluated by ultrasounds (height, width, volume and surface area) at birth and every weeks after birth (measures in NIUG =372; in RIUG = 81). The lipids content of brain and cerebellum (LCB expressed in % of CM) was estimated from its volume, mass according to Siri's equation. The growth of skeletal muscles (MM) was calculated by the urinary excretion of creatinine and by the mid left arm muscle circumference (LAMC). The subcutaneous adipose tissue (TS) was measured by the skin fold method at the mid left arm. The metabolic balances (n=264) were performed over 3 days. The range of study was 4 to 40 days of life.

## Results

The intakes per kg BW in calories, proteins, lipids, carbohydrates and fluids were the same in both groups. The caloric cost for weight, brain, muscles and length was higher in the RIUG sample, but was the same for HC in both groups. The postnatal weekly increase was higher in NIUG concerning BW, MM g, LAMC. It was similar in both groups for BL, HC and TS. The caloric cost of growth for brain, length, muscles was higher in RIUG neonates. The growth of cerebellum was lower in RIUG all time, but increased significantly after birth in these infants. The lipids content in % of brain was higher in RIUG than NIUG babies in fetal period and after birth. When comparing the efficiency of proteins in different milks, the highest for HC was found with human milk.

## Conclusions

The differences between NIUG and RIUG observed could be explained by the quantitative and qualitative differences during fetal and postnatal lives in intakes (amino acids, carbohydrates, lipids), by the priorities and the cost for growth due to different tissues during fetal and postnatal lives, and by the insulin influence among these periods of life.

## **Introduction**

The importance of growth during the fetal and postnatal periods has been established for the infant's future since many years. For the children might be concerned in their developmental, cardiovascular, immunological, renal and metabolic outcomes [1-35]. That concept has been confirmed by animal studies and by clinical follow-up cohorts of babies at risk. From a physiological point of view, the starting point can be the restriction of blood flow through the placenta leading to a restricted or retarded intrauterine growth (RIUG) or an inappropriate postnatal nutrition or perfusion in different organs (restricted or retarded extrauterine growth or REIG). These consequences are mediated by the restriction of amino acids delivery to the fetus, the inappropriate postnatal (hyper or hypo) nutrition, the response of the renine – angiotensin – aldosterone complex, the reduced activity of the 11-hydroxysteroid dehydrogenase, the reduced NO-dependent vasodilatation response, the increased activity of adrenergic system, the reduction in nephrons production in case of important prematurity, the acute or repetitive inflammation cascade. We conducted a prospective and longitudinal study in premature neonates well fed according to the international recommendations for oral or intravenous routes. We centered our analysis on their perinatal growth of brain, cerebellum, subcutaneous adipose tissue and skeletal muscles beside the classical parameters as the weight, the length, the head circumference. These tissues combine the dependency or independency from insulin activity on one hand, and also they have an important quantitative and qualitative place on the other hand. We wanted to determine the postnatal priorities among these selected tissues.

## **Methods**

### **Study setting and subjects**

This study was approved by the Ethical Committee. The population comprised 150 premature babies without malformations, birth asphyxia or respiratory distress syndrome. This cohort represents the “fetal life” sample. It was divided in two groups (Table 1): the babies having experienced a normal intrauterine growth or NIUG, and those who had a retarded or restricted intrauterine growth or RIUG. The RIUG is a difficult parameter to define and we recently discussed that point in other works [36-40]. In this study, owing to a protocol in the Belgian group of neonatal intensive care units, RIUG was defined as a birth weight or a ponderal index

below the 10<sup>th</sup> centile according to Lubchenco's neonatal charts.

**Table 1.** *The "fetal life" sample or the population studied at birth.*

	NIUG	RIUG
N	125	25
Birth weight g	1858 ± 574	1454 ± 559
Gestational age weeks	32.7 ± 2.9	33.9 ± 3.95

That population was then prospectively followed during the neonatal stay, representing "the postnatal population sample (Table 2). The primary concept of NIUG and RIUG was maintained in their individual trajectory throughout the hospital stay.

We had to discard 23 (18.4 %) from NIUG and in 7 (28 %) from RIUG infants owing the difficulties during their metabolic balances.

**Table 2.** *The sample of population of the postnatal period.*

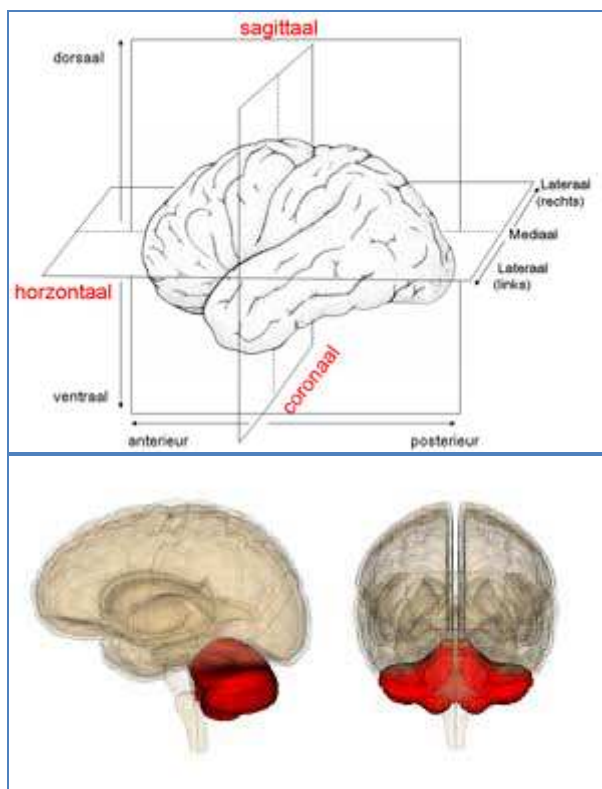
	NIUG	RIUG
N babies	102	18
N measures	372	81

### **Study procedures**

The gestational age at birth was determined according to the late menstrual periods and by the Finnström clinical method and the different methods of anthropometric measurements applied the usual recommendations [36-76]. The measurements reflecting the fetal period were done as early as possible and anyway within the first 6 hours of life. The postnatal measurements and calculations were done every week afterwards.

**The anthropometric clinical and echo graphic measurements** comprised the body weight (BW), the body length (BL), the head circumference (HC). At the mid left arm: circumference (LAC), triceps skin fold (LATS), and the derived muscle circumference (LAMC cm = LAC cm - 0.314 LATS mm). The cerebral mass (CM) was calculated from HC according to Dobbing formula [13, 14, and 48]:  $CM\ g = [(HC^3)/100] - [1500/HC]$ . The parameters measured by ultrasounds were (Figure 1): from coronal and lateral cuts at the level of third ventricle the height of frontal lobes and the hemispheric area and volume; from posterior coronal and lateral cuts the height, width and surface area and volume of cerebellum.

**Figure 1 .** The intracranial structures are visualized and measured through anterior and posterior fontanelles in their different dimensions (coronal, horizontal and sagittal cuts).



The in vivo tissue lipids' content (LCT) was estimated from the LATS and from Siri's formula [14] that takes into account the density and volume of tissues:  $LCB\ \% = [(Volume/CM)*495 - [450]$ . The body skeletal muscles mass or MM was calculated from the creatinine excretion in urines [42, 45].

**The metabolic balances** were done during 3 consecutives days concerning the intakes (intravenous and or enteral routes) and the losses (in stools and in urines). The basal metabolic

rate was calculated from the continuously record of heart frequency according to Chessex and collaborators [46, 50]. The dosage of proteins was done by Kjeldhal method, the dosage of lipids by the method of Sperry, and the dosage of carbohydrates by HPLC chromatography. The dosage of insulin and C-peptide was made by radio-immunoassay. The **coefficient of efficiency of proteins for growth** (CEP) is the ratio of what was obtained in growth divided by 100 g of proteins intake. This could be done for the HC, the BW, and the BL.

The **caloric cost of growth** was calculated for the body, the brain and the skeletal muscles.

## Results

Concerning **the intakes** expressed /kg BW/day, the comparison between NIUG and RIUG evidenced none differences. The averaged values were:  $127.5 \pm 22.5$  kcal,  $3.4 \pm 0.8$  g of proteins,  $18.2 \pm 3.5$  g of carbohydrates,  $5.1 \pm 1.3$  g of lipids, and  $161 \pm 17.4$  of fluids.

In both groups, we found significant ( $p < 0.05$ ) correlations coming out the analysis of **the metabolic balances** as authors in previous studies [45-50]. The correlations having a very strong force of association ( $r^2 > 0.8$ ) were:

- Between caloric intakes and  $\Delta$  BW ( $= 0.23$  cal intake  $- 19$ ,  $r^2 = 0.98$ )
- Between proteins intakes and  $\Delta$  BW ( $= 3.4$  P intake  $+ 7.3$ ,  $r^2 = 0.81$ )
- Between proteins intakes and  $\Delta$  HC ( $= 0.6$  P intake  $+ 0.25$ ,  $r^2 = 0.84$ )
- Between proteins intakes and  $\Delta$  BL ( $= 0.34$  P intake  $+ 0.253$ ,  $r^2 = 0.82$ )
- Between blood levels of insulin micro U/ml and of glucose mmol/100 ml ( $= 3.75$  -2.3 G,  $r^2 = 0.81$ )
- Between C-peptide in urines Pico mole/kg/d and carbohydrates intake g/kg/d ( $= 60$  CH intake  $+ 200$ ,  $r^2 = 0.98$ )
- Between gestational age and BMR kcal/kg/d ( $= 0.79$  GA  $+ 18.6$ ,  $r^2 = 0.98$ )
- Between GA and Pt % BW ( $= 0.257$  GA  $+ 1.766$ ,  $r^2 = 0.81$ )
- Between GA and Lip % BW ( $= 0.811$  GA  $- 19.5$ ,  $r^2 = 0.97$ ).
- Between the ratio  $(100 * \text{LAC})/\text{HC}$  and gestational age ( $= 0.56$  GA  $+ 6.5$ ,  $r^2 = 0.83$ )

We found also other significant correlations but with a weaker force of association ( $r^2 < 0.6$ ):

- Between Pt synthesis and BMR ( $= 0.173 \text{ BMR} - 2.56$ ,  $r^2 = 0.5$ )
- Between Pt accretion and BMR ( $= 0.011 \text{ BMR} + 1.559$ ,  $r^2 = 0.21$ )
- Between LAC and GA ( $= 0.26 \text{ GA} - 1.685$ ,  $r^2 = 0.52$ )
- Between muscles body content or MM % BW and body weight ( $= 29.8 - 1.8 \text{ BW kg}$ ,  $r^2 = 0.36$ )
- Between MM % BW and LAC ( $= 44.63 - 2 \text{ LAC}$ ,  $r^2 = 0.4$ )
- Between TS and GA ( $= 0.078 \text{ GA} + 0.47$ ,  $r^2 = 0.25$ )

About the **global and focalized postnatal growth**, interesting results could be underlined concerning the weekly assessment or  $\Delta$  of different parameters. We observed differences in the  $\Delta$  BW and MM who were significantly higher in the NIUG babies, and no differences in the other parameters of growth. The **caloric cost** of growth concerning BW, BL, brain and muscles was significantly higher in the RIUG babies (Table 3).

**Table 3.** *The postnatal growth of tissues*

	NIUG	RIUG	P
$\Delta$ BW g	181± 82	133± 76	< 0.05
$\Delta$ BL cm	1 ± 0.57	1 ± 0.74	> 0.05
$\Delta$ HC cm	0.8± 0.34	0.75± 0.34	> 0.05
$\Delta$ LATS mm	0.6 ± 0.59	0.5 ± 0.48	> 0.05
$\Delta$ LAMC cm	0.31± 0.56	0.26 ± 0.52	> 0.05
$\Delta$ MM g	41.6 ± 10	28 ± 5.6	< 0.001
Caloric cost /g BW	4.8±0.5	5.9±1	< 0.05
Caloric cost / cm BL	798 ± 40	1275 ± 145	
Caloric cost/g brain	0.55±0.05	1.3±0.23	< 0.01
Caloric cost/g MM	0.8±0.08	1.35±0.24	< 0.01

What **the growth of brain and cerebellum** is concerned, the babies in NIUG group had higher values in the indices of growth for cerebellum but not for brain during the fetal period. In the postnatal period, NIUG had higher values than RIUG for cerebellum and brain. But within the RIUG group, the comparison of their growth of brain and cerebellum evidenced a significant improvement of cerebellum growth in the postnatal period (Table 4).

**Table 4.** *The brain and cerebellum indices of growth*

	NIUG	IUG	P
<b>Cerebellum</b>			
$\Delta$ width mm /week			
- utero period	1.75± 0.24	0.7 ± 0.12	< 0.01
- postnatal period	1.75 ± 0.3	1 ± 0.18	< 0.01
$\Delta$ area mm <sup>2</sup> / week			
- utero period	6.3 ± 0.9	5 ± 0.9	< 0.05
- postnatal period	110 ± 15	85 ± 11.9	< 0.01
<b>Brain</b>			
hemispheric growth (mm)			
- utero period	0.926 HC – 5	0.98 HC – 5	> 0.05
	0.675 GA +1.09	0.8 GA -4.2	> 0.05
- postnatal period	0.864 GA – 5.4	0.8 GA – 4	< 0.05
	0.925 HC – 4.9	0.92 HC – 4.7	> 0.05

It was also interesting to note that the **lipid content of brain and cerebellum** was higher in the RIUG: both in the fetal life and in the postnatal period (Table 5). Again, the comparison of their fetal and postnatal period showed a significant decrease (and more similar to what was observed in NIUG group) of LCB in the RIUG.



**Table 5.** The Calculated lipids contents of brain (LCB expressed in % of CM) according to measured head circumference (HC expressed in cm). Regression lines with SD and  $r^2$

	LCB in % CM NIUG	LCB in % CM RIUG	P
In utero sample	0.633 HC + 6.57 (sd =6.57, $r^2$ 0.98) (n=125)	0.675 HC+ 7 (sd = 3.8 $r^2$ 0.98) (n=25)	< 0.01
Postnatal sample	0.5 HC + 5.4 ((sd = 2.6, $r^2$ 0.98) (n=372)	0.54 HC+ 5.6 ( sd =3 $r^2$ 0.98) (n=81)	< 0.01

In the babies, some were completely fed by mother's milk (HM), other by adapted formulas for prematurely (PTF) or term newborns when approaching 37 weeks (TF). For head circumference or HC, the CEP was higher for HM:  $3.9 \pm 0.5$  versus  $3.3 \pm 1$  for PTF and  $3.4 \pm$  for TF ( $p < 0.05$ ).

What the **synthesis of MM** is concerned, the NIUG for a similar fetal gestational age had a greater content of MM then RIUG babies. In the postnatal period, NIUG made more muscles than RIUG babies, either in enteral or parenteral feeding. But proportionally to BW, the increments were similar. Within the NIUG group, the synthesis of MM was higher in the postnatal period and during the enteral feeding. In the RIUG, the synthesis remained similar when fetal and postnatal periods were compared (Table 6).

**Table 6.** *The muscles mass (MM g) according to measured body weight in g (BW) or gestational age (GA in weeks) and according to the mode of feeding.*

	NIUG	RIUG	p
<b>« fetal sample »</b>	MM g	MMg	
	0.18 BW – 55 (r <sup>2</sup> =0.25)	0.29 BW -79.7 (r <sup>2</sup> =0.25)	< 0.01
	44.51 GA -1050 (r <sup>2</sup> =0.37)	30.46 GA - 708 (r <sup>2</sup> 0.36)	< 0.01
<b>Postnatal sample</b>			
<b>- enteral feeding</b>			
<b>MM g</b>	0.26 BW – 41.45 (r <sup>2</sup> =0.6)	0.28 BW – 80 (r <sup>2</sup> =0.34)	< 0.01
<b>MM g/week</b>	30.5 ± 4	25 ± 6	< 0.01
<b>MM % BW</b>	26± 3	21 ± 3	< 0.01
<b>- parenteral feeding</b>			
<b>MM g</b>	0.21 BW – 12.4 (r <sup>2</sup> = 0.54)	0.27 BW -50.3 (r <sup>2</sup> = 0.56)	< 0.01
<b>MM g/week</b>	34.4 ± 6	27 ± 5	< 0.01
<b>MM % BW</b>	20.4 ± 4	22 ± 5	> 0.05

## Discussion

The importance of growth during the fetal and postnatal periods has to be considered for the future for the points might be concerned in babies' developmental, cardiovascular, immunological, renal and metabolic outcomes. Very important studies have been done during the period going from 1980 to 2000 [1-37, 48, 50-78]. This can be explained by the facts that, at that time, many questions emerged about the qualitative and quantitative optimality of nutrition owing to the neonatal period and the outcome of babies who were born more and more premature. We can also recognize the tremendous energy devoted by some groups to these questions, evidenced by the numerous publications. The follow-up studies, but also the epidemiology on adults' situations pointed the antenatal and neonatal situations as the probable source of explanation for longer outcome in the developmental, cardiovascular,

immunological, renal and metabolic findings [1,3-5,7,9-13,18,24,28,30-35, 79, 80]. Beside these facts and also thanks to the development of new non aggressive techniques, this translational approach (which goes from humans to animals investigations and their feedback) stimulates research to refine the therapeutically approach of newborn babies at risk of difficult outcomes. This study brings more arguments about the importance of the foetal period and the consequent neonatal period. We recognize that the concept of intrauterine growth retardation is a major and difficult point. We can also underline that the observed postnatal retarded growth in neonates, particularly in very premature babies not having experienced a RIUG, is another difficulty of understanding: does that reveal after birth a mechanism began in utero? If we consider our observations about cerebellum and brain, we can say that: i. the growth of cerebellum is lower in the RIUG in both considered periods; ii. The growth of cerebellum and brain in RIUG is better after birth; iii. The growth of brain is slightly lower in RIUG in the postnatal period; iv. The higher LCB observed in RIUG in both periods but mainly in foetal life as that decrease in the postnatal period, can be explained by the de novo synthesis of lipids from carbohydrates. Indeed, when blood flow is reduced, the delivery of oxygen and amino acids is more pronounced than the delivery of glucose. We don't know actually the part of that in what is observed in the outcome of babies at risk [80]. If, in the postnatal period, we consider moreover the accretion of weight, length, head circumference, muscles, we can conclude, from the observed results in NIUG and RIUG, that priority is given to the brain and cerebellum, these tissues being more independent than the muscles of insulin action on glycoregulation. These facts explain the different caloric cost for growth observed.

It was also interesting to note that, although the quantity of proteins offered to the babies was similar, the proteins of human milk were more efficient to promote the growth of brain as reflected by the head circumference. This might be due not solely to the quality of human milk, but also to other factors present in human milk.

## **Conclusions**

The differences between NIUG and RIUG observed could be explained by the quantitative and qualitative differences during fetal and postnatal lives in intakes: blood flow, delivery of oxygen, amino acids, carbohydrates, fatty acids. The priority for growth during fetal life remains the central nervous in the postnatal life. The cost for growth of different tissues reflects that priority. The observed postnatal retarded growth in very premature NIUG might

reveal a mechanism present before birth. Human milk, more than solely the quality of proteins, is the most efficient nutriment for brain growth.

**This work is dedicated to our deceased friend and collaborator Dr Leon Withofs.**

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