THE FETAL BRAIN AND INTRAUTERINE GROWTH RETARDATION

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The importance of the search for factors influencing intrauterine growth is well illustrated by the high rate of perinatal mortality in small-for-date children. The relationship between impaired intrauterine growth and high perinatal mortality appears from fig 1. Children with a birth weight below the 2.3 percentile line account for 31% of the total number of perinatal deaths (17).

Perinatal mortality was defined as death within a week after birth. It was calculated for those children born after 28 weeks or more of pregnancy. The data are based on 8,406 births in the years 1965-1968 in the Wilhelmina Gasthuis, Amsterdam, Department of Obstetrics and Gynaecology (head: Prof. Dr. G.J. Kloosterman), from which 7,665 could be placed into the percentile groups. Perinatal mortality took place in 310 cases, of which 291 could be placed into the percentile group. Perinatal mortality is expressed as a percentage of the total number of births in each group. Note the high percentage of perinatal mortality in the lowest percentile group. The broken line indicates the overall perinatal mortality rate in this group. The data were collected by Miss B.L. Huidkoper (from 17, with permission).

Figuur 1  The relation between perinatal mortality and birth weight in man.

The present paper will deal with two aspects. In addition to a dis-
discussion of the maternal (e.g. vascular) and environmental factors thought to be causal in intrauterine growth retardation, two questions in relation to a fetal factor and more specifically to the fetal brain seem warranted, namely

- whether there is an endogenous brain factor which normally stimulates fetal growth and whether this factor might be absent in some cases of intrauterine growth retardation. The existence of such a putative factor has obtained little or no attention lately, neither from our own research group nor in the literature.

In the second part of this paper attention is paid to

- the important point of the possible existence of critical periods in fetal brain development and the consequences of growth retardation of the fetal brain. The relevance of this topic has recently become more and more apparent because of the high percentage of neurological handicaps in dysmature children.

**Fetal growth retardation in congenital brain anomalies**

Normal fetal growth in man is characterized by an S-shaped curve. An acceleration of fetal growth rate takes place around 20 weeks of pregnancy (20; Fig. 2a). This intrauterine growth spurt depends on the integrity of the fetal brain, as is apparent from the diminished growth rate found in human anencephalics. In this congenital anomaly, which develops in the 3 to 4-week-old fetus, the cranial vault is absent. The cerebral hemispheres are either completely missing or reduced to small masses, and the hypothalamus is usually absent (12). Jost (8) has emphasized that intrauterine growth does not stop in human anencephalics and, after decapitation, in fetuses of various species. He was right, (Fig. 2a), yet a clear growth retardation, starting around the moment of the intrauterine growth spurt, is found in anencephalics (5). At 40 weeks of pregnancy the mean anencephalic birth weight - corrected for brain weight - is 1000 g lower than normal. Some growth impairment also exists in other congenital anomalies, but the growth retardation in anencephalics is much more marked (16). Data obtained following surgical encephalecctomy in rhesus monkey were strikingly similar to the ones obtained in anencephalics (9; Fig. 2b).

The idea that the intrauterine growth spurt is stimulated by a factor originating from the brain is reinforced by data from two case histories (7,10) of spontaneous decapitation (probably due to strangulation during the first trimester), and from two microcephalics in which the hypothalamus was absent. In all four cases birth weights were as low as in anencephalics (Fig. 2a). Therefore, experiments in rat were performed in order to find hypothalamic factors that might stimulate intrauterine growth.

Fig. 2 shows the influence of the fetal brain on intrauterine growth in man (a) and rhesus monkey (b).

a) Birth weight against length of gestation for 121 human anencephalics; 50th centile line of the control group (50); 50th centile line of the control group after subtraction of mean brain weight (B). The characteristics of the linear regression lines for male and female anencephalics are given in the
Figuur 2 The influence of the fetal brain on intrauterine growth in man (a) and rhesus monkey (b).

left upper corner (based on the material described in 5). In addition, data are provided for two (x) non-macerated cases of spontaneous fetal decapitation and two (●) cases of microcephaly in which the hypothalamus was absent. The body weights are corrected so that they can be compared to the anencephalic regression lines (x = decapitated body weight plus head weight minus brain weight; ● = body weight minus brain weight). Note that in these three anomalies that lack the hypothalamus fetal body weight is low.

b) Body weight against length of gestation for normal (c), decapitated (I) and decerebrated fetal rhesus monkeys (pituitary island, II). (Reproduced from (9) with permission of the Ciba Foundation.) Note the similarity between the intrauterine growth pattern in the experimental animals and human anencephalics in Fig. 2a (from 20).

Fetal brain and intrauterine growth
During normal intrauterine development, fetal growth in the rat shows a sudden acceleration at day 19 of pregnancy in a way similar to that seen around 20 weeks of pregnancy in the human fetus. This growth spurt appeared to be absent in rat fetuses from which the brain and pituitary had been removed (15,16). A reduction in fetal body weight has also been found following selective destruction of the fetal rat hypothalamus (2) and following fetal hypophysectomy (1,10). In order to test the possibility that humeral factors of hypothalamo-hypophysial origin play a role in the regulation of intrauterine growth, pituitary hormones or hypothalamic extracts were injected directly into rat fetuses whose brain and pituitary had been removed and fetal weight was measured two days later. No stimulation of intrauterine growth was obtained with any of the following compounds:
growth hormone, ACTH 1-24, ACTH 4-10, TSH, prolactin, LH, FSH, HCG, oxytocin, hypothalamic extract (Fraction C), insulin, placenta extract and cyclic AMP (6,16). The only factor which was found to stimulate intrauterine growth was α-MSH (6,16).

**α-MSH and fetal growth**

α-MSH is a pituitary peptide which is present at least from day 18 of pregnancy, i.e. one day before the intrauterine growth spurt in rat takes place. Injection of an antibody agonist α-MSH directly into the rat fetus inhibits intrauterine body and brain growth (18,20). This observation indicates that fetal growth stimulation of α-MSH is not only an effect of this peptide but possibly also a natural function of the endogenous hormone. In the human fetus, α-MSH was found to be present in the intermediate and anterior lobe of the pituitary from at least 15 weeks of pregnancy onwards (14,22), but to be absent in anencephalic fetuses. An interesting observation in this context was that the human fetal pituitary has a distinct intermediate lobe. This fetal pars intermedia that contains α-MSH is gradually transformed during postnatal development into an adult "zona intermedia". This structure consists of the former pars intermedia, which is frequently interrupted by cysts. In the adult zona intermedia less α-MSH and more ACTH-containing cells were found (22). This postnatal change of the pars intermedia suggests a special role for this structure and for α-MSH in fetal development. The absence of the pars intermedia and α-MSH in human anencephalics (22) is consistent with a stimulating role for α-MSH in intrauterine growth in man. The mechanism by which α-MSH stimulates intrauterine growth, the fetal brain factor stimulating the release of α-MSH, and the question whether decreased release of α-MSH is present in particular cases of intrauterine growth retardation still have to be studied. An alternative explanation for the observations is that the fetal factor stimulating intrauterine growth (i.e. α-MSH or another factor) comes directly from the brain, since children with a congenital pituitary aplasia may have normal birth weights and the brain contains α-MSH and related compounds (16,17).

**Fetal growth retardation and the brain**

Neligan et al. (13) published a first extensive follow-up study in which he showed that children who are born too small (light for dates, dysmatures) show a long-term impaired intellectual performance. The degree of intrauterine growth impairment was proportional to the degree of later performance, suggesting a direct relationship. The overall performance of the dysmature children was worse than that of the prematures. Boys appeared to be more vulnerable to the adverse effects of abnormalities of intrauterine growth than girls; this was found to hold for temperament, behavior, neurological abnormality scores and the measurements of physical growth. In her thesis, Hadders-Algra (3) reviewed later long-term follow-up studies that essentially confirmed these findings. Infants with severe intra-uterine growth retardation appear to be at risk for developmental deviances, e.g. major and minor neurological dysfunction, lower IQ scores, speech-langua-
ge problems and behavioral and educational problems such as attention-deficit disorders. The hypothesis of the etiology of these impairments that has been proposed is that inadequate fetal nutritional supply induces central nervous system developmental disorders in a period of rapid brain development (3). Usually male infants are found to be at a disadvantage, which is an interesting point in relation to the presence of sex differences in the human brain (21). The results of Hadders-Algra (3) suggest the temporal presence of a difference in potentially harmful factors: for neurological handicaps early in pregnancy, for minor neurological dysfunctions the second half of gestation and the first two years of life.

**Intrauterine growth retardation as a neurological symptom**

Neligan et al. (13) already revealed the striking relationship between prenatal impairment of growth and later impairment of performance. The finding that these two phenomena are proportional asks for an explanation. As discussed in the first part of this paper, the fetal brain probably produces growth factors that are responsible for the acceleration of intrauterine growth around 20 weeks of pregnancy. In relation to this, we propose that impaired intrauterine growth can be considered as an early symptom of impaired brain development and function that will not lead to impaired intellectual performance until much later.

Similar reasoning may hold for the occurrence of premature or postmature deliveries and disturbed course of labor. The fetal brain determines to a certain degree both the moment and the course of labor (4,17). Consequently, pre-maturity and post-maturity or an impaired course of labor may be symptoms of suboptimal development of neuronal symptoms.

In conclusion, the fetal brain is actively involved in intrauterine growth and labor. Therefore, impairment of these processes may, at least sometimes, be an early sign of impaired fetal brain functional development. This hypothesis may be a good reason to plead for a close relationship between the obstetrical clinic’s neonatal care unit and developmental neurologists, both clinicians and fundamental neuroscientists. A basis for such a multidisciplinary approach has been laid by Prof. G.J. Kloosterman and Prof. dr. P.E. Treffers.

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**References**

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