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WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES No. 540

Maturation of Fetal Body Systems

Report of a WHO Scientific Group

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

GENEVA
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* * *

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CONTENTS

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CONTENTS

WHO SCIENTIFIC GROUP ON MATURATION OF FETAL BODY SYSTEMS

Geneva, 21–27 August 1973

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MATURATION OF FETAL BODY SYSTEMS

Report of a WHO Scientific Group

A WHO Scientific Group on Maturation of Fetal Body Systems met in Geneva from 21 to 27 August 1973. The meeting was opened by Dr W. H. Chang, Assistant Director-General, on behalf of the Director-General.

1. INTRODUCTION

An infant that is mature at birth may be defined as one that shows functional competence, providing a reasonable safety margin, in the environmental and other circumstances to which it is normally exposed. For immediate survival the cardiovascular, respiratory, thermoregulatory, and endocrine systems must be competent. It is not essential that the skeletal muscles, other than those with respiratory functions, or the distance receptors, auditory or visual, should work well at birth. Immunological competence is vital, especially where passive protection is not available.

The different organ systems mature at different rates during gestation. An effective circulation must be established with placentation, but the lungs and kidneys are not needed for survival until birth, though they may be necessary for normal fetal development. In the intermediate period the fetus is not an inactive passenger *in utero*. It shows a wide variety of nervous and muscular activities, including breathing movements, that become increasingly vigorous and varied with age ; for these the circulatory, metabolic, endocrine, and nervous support systems must be provided. Measurement of each of these and further study of their integrated function is required, as well as an appreciation of the determinants of growth, for a good picture of maturation. In some instances natural perturbations may be used to assess the ability of the fetus to participate in maintaining its environment and to grow in relation to functional and pathological changes. Such an opportunity is afforded by premature delivery, with reservations related to the cause of the onset of labour where they are known.

The relative inaccessibility of the fetus, which is such an important feature of its defence mechanisms, has been a major barrier to systematic scientific study. While acknowledging the considerable contributions of classical embryology, biochemistry, and physiology, it should be noted that animal studies, particularly in the last 15 years, have established a new framework of knowledge that has illuminated hitherto obscure perinatal disease. But our knowledge is still fragmentary.

The objectives of this Scientific Group were (1) to identify, in relation to selected body systems and within the special fields of expertise of the participants, some areas in which lack or disorder of maturation contributes to the excess morbidity and mortality of the human infant, and (2) to review current methods of assessing this maturation before and after birth in the human and to define the control mechanisms, maternal and fetal, where these are known. The Group then reviewed selected animal studies that have given and continue to give insight into the control and assessment of maturation, particularly when relevant studies in man are ethically or technically impossible. The Group discussed some of the difficulties that are encountered in interpreting the results of nonhuman studies in relation to the human fetus and infant. Throughout the text, areas of probable or possible future development are presented. Finally, specific recommendations are made for future studies on animals and humans.

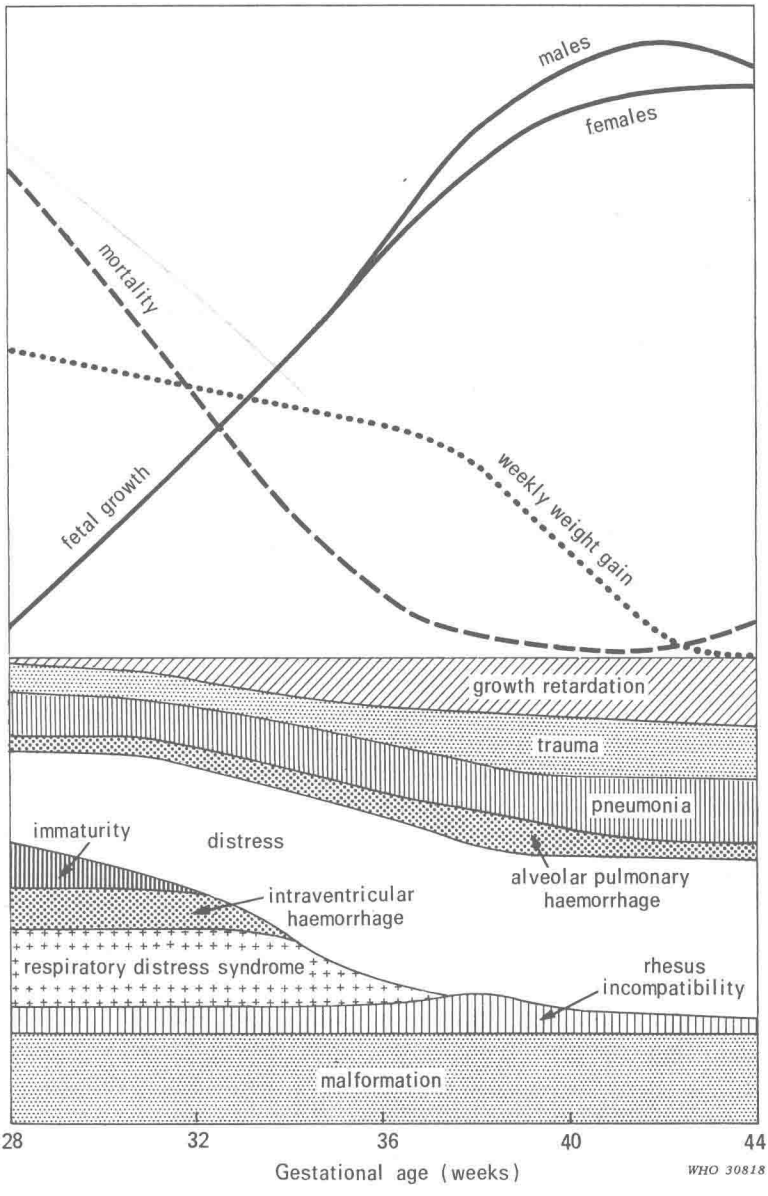
2. COMMON CLINICAL PROBLEMS

The British Perinatal Mortality Survey has provided invaluable information in connexion with causes of death. It was noted in the second report[1] that "... maturation is prominently associated with gestational age, as has been amply demonstrated by clinical as well as postmortem studies ... Since various biological functions mature at different times, the incidence of pathological conditions caused by one or another aspect of immaturity (in conjunction with external agents) varies with different gestational ages." The proportions of abnormalities found at autopsy in infants of different gestational ages are shown in the accompanying figure. Conditions associated with immaturity would be expected to be more prominent at 28 weeks than at 40 weeks. Note that intraventricular haemorrhage and the respiratory distress syndrome are the only two conditions, other than "immaturity" itself, that are restricted to infants of lower gestational ages.

It is a complex problem to decide which malfunctions are limiting to life, and to determine the causes of morbidity and mortality. The clinician faces the paradox that some infants born after short gestations of 26–28 weeks, and of accordingly low birth weight, appear to have an uncomplicated postnatal course. Others born at 36 weeks, also of appropriate weight, may have evidence of immaturity of one or more organ systems. It is now recognized that body weight is not always an appropriate guide

[1] Butler, N. R. & Alberman, E. D. (1969) *Perinatal problems. The Second Report of the 1958 British Perinatal Mortality Survey*, London, E. & S. Livingstone Ltd.

INCIDENCE OF SPECIFIC CAUSES OF DEATH AND BASIC DATA ON FETAL GROWTH AT DIFFERENT GESTATIONAL AGES[1]



[1] From: Butler, N. R. & Alberman, E. D. (1969) loc. cit.

to gestational age, or *vice versa*. While fetal growth charts depict the percentiles for weight at different gestational ages, significant departures from predicted growth are now commonly acknowledged, for example, after certain fetal insults, such as rubella, after restriction of placental blood flow in the experimental animal, or in association with a number of congenital malformations. Only recently has it been recognized that in a given infant the degree of maturation of any one organ system could be relatively accelerated or delayed.[1]

The incidence of conditions that contribute to perinatal morbidity may vary widely in different parts of the world, but premature onset of labour is a major factor everywhere, with highest mortality in the more immature infants.

Maternal factors that are associated with high risk to the infant include infections, malnutrition, hypertension, abnormalities of the uterus, cephalopelvic disproportion, cord accidents, and placental abruption. Adverse fetal–maternal interactions can occur as in isoimmunization of the mother by fetal antigens.

Disorders that may have their genesis *in utero*, but express themselves in the newborn infant, include hyaline membrane disease, pulmonary haemorrhage, intraventricular haemorrhage, haemolytic disease of the newborn, and structural and functional malformations. Longer term consequences include, for example, neural and muscular disorders.

Acquired neonatal disorders are much more frequent in the prematurely born, and include infection, haemorrhage, and apnoeic spells, but at times death occurs in the absence of other detectable changes. Undersized infants have little fat, and thus are dependent on adequate calorie intake. Appropriate feeding is hard to achieve in very small infants, in part because of lack of knowledge of the best food to provide, and in part because the immature gastrointestinal tract may not absorb food adequately. Necrotizing enterocolitis is an increasing problem among babies with low birth weight who survive their initial respiratory distress and live for 2 or 3 weeks. Another major problem among these infants is persistent patency of the ductus arteriosus, occasionally leading to heart failure.

Systematic observations on prematurely born infants can define the extent of functional immaturity, the processes that " mature " faster as a result of birth, and life-limiting malfunctions. Further delineation of the chemical stages of maturation, discovery of regulators of maturation, and knowledge of the long-term effects of forcing differentiation either pharmacologically or by premature delivery should permit improved management of immature infants.

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[1] Kotas, R. V. et al. (1971) Evidence for independent regulators of organ maturation in fetal rabbits, *Pediatrics*, **47**, 57.

3. REGULATION OF FETAL GROWTH AND PLACENTAL COMPETENCE

The size and weight of the mature infant vary widely in most of the species studied, especially those with long gestations. Divergence in growth rates takes place mainly in the latter half of pregnancy and is influenced by different genetic and environmental factors. While there exists a general correlation between the weight of the infant and that of the placenta, significant exceptions can be found and placental weight cannot be considered a reliable indication of fetal growth. Thus, while the placental growth curve in sheep and in man flattens much before term, the development of placental structure and transfer continues along with fetal growth. Whether changes in placental function in late pregnancy become rate-limiting to fetal growth is not yet known. Observations in sheep and in man suggest that the transfer function of the placenta is sufficient to support fetal life well after term.

Regulatory factors affecting fetal growth are manifold and have a quantitatively different impact. An order of importance has been proposed [1] for the effect of these factors on the human fetus as follows: (*a*) intrauterine and fetal environment, (*b*) maternal genotype, (*c*) maternal environment, (*d*) fetal genotype, (*e*) parity, (*f*) maternal health and nutrition, (*g*) sex of fetus, and (*h*) maternal age. Experimental studies in animals support, in general, these deductions but have also led to the recognition of some factors not yet studied in man.

Infants of low birth weight, other than immature (preterm) infants, present a common paediatric problem. Attempts made to separate them into classes, such as growth-retarded (dysmature) and small for gestational age infants, have not led to a standard nomenclature. Such aberrations in growth, almost exclusively reductions, may result from infections, teratological influences, chromosomal errors, maternal malnutrition, high altitude, and other factors.[2] Prominent among the factors leading to fetal growth retardation, however, are maternal pre-eclampsia and multiple births, particularly the birth of monozygous twins. In pre-eclampsia it is believed that growth retardation results from a reduction of maternal placental perfusion with subsequent reduction in the placental exchange surface. Similar mechanisms cause retardation in some of the haemoglobinopathies. On the other hand, the severe growth retardation in one of a pair of monozygous twins with the " transfusion syndrome " is attributed to haemodynamic changes in the fetal–placental vascular system.

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[1] Penrose, L. S. (1961) *Genetics of growth and development of the fetus.* In : Penrose, L. S., ed., *Recent advances in human genetics*, Boston, Little Brown & Co.

[2] McClung, J. (1969) *Effects of high altitude on human birth*, Cambridge, Mass., Harvard University Press.

Many infants with prenatal growth restriction remain permanently growth-retarded despite adequate postnatal nutrition.

The methods used to assess fetal growth in man fall into two main categories, those that measure fetal size and those that depend on maturation of particular fetal body systems. The latter usually reflect total fetal growth, but may not do so in abnormal circumstances.

Few clinicians have confidence in their ability to determine fetal size accurately by palpation. Serial radiological studies cannot be supported because of their inaccuracy and potential fetal hazard. Measurements with ultrasound are probably the best available means of estimating fetal size and growth ; sequential measurements of trunk size and skull size improve accuracy.

The value of measuring the maternal blood levels, or the urinary output, of a variety of compounds has been explored. For example, it has been known for many years that there is a statistical relationship between urinary pregnanediol excretion and fetal growth. Individually, the relationship is not sufficiently close for useful clinical purposes. Serial measurements of urinary estriol and perhaps estetrol continue to provide information of some value in high risk pregnancies. They have a reasonably close relationship with fetal growth and particularly with changes in fetal growth. The value of assay of these hormones in maternal plasma is not yet clear. Assay of human chorionic somatomammotrophin should, as far as is known, be regarded as complementary to, rather than an alternative to, measurement of estriol. The large amount of data available on changes in some enzymes has not been of significant assistance. In pre-eclampsia, serial measurement of fibrinogen degradation products may be useful.

The clinical usefulness, in the assessment of fetal growth, of determining the levels of amniotic creatinine, bilirubin, and the proportion of fat-staining cells has not been firmly established. Measurements of lecithin or lecithin–sphingomyelin ratios, perhaps together with assay of amniotic cortisol, are very useful in assessing maturation of the lungs.

Many animal species have been employed in the search for answers to the specific growth-limiting factors in fetal development. In an early experiment on crossing Shire horses and Shetland ponies [1] the size of the newborn foal was thought to be a reflection of that of the dam. The inference drawn from this study that maternal size has a large influence on fetal size—estimated by some to be responsible for 50–75% of fetal size variability—is not uniformly accepted and the mechanisms are not clear. Many are of the opinion that nutrition, in the larger sense or in the restrictive sense of uterine perfusion, limits fetal size, either by limiting

[1] Walton, A. & Hammond, J. (1938) The maternal effects on growth and conformation in Shire horse–Shetland pony crosses, *Proc roy. Soc. B.*, **125**, 311.

fetal and placental growth, or by limiting placental growth and thereby fetal growth.

Reduction of uterine vascular perfusion has been achieved by ligation of arteries in rats and a few other species.[1] It may lead to severe fetal stunting but more quantitative measurements of the relationships of reduced flow to fetal growth restriction are needed. Similar effects may be seen in maternal treatment with vasoconstrictive drugs.

Severe growth retardation can be achieved in rhesus monkey and sheep fetuses when the size of the fetal placenta or of the placental vascular bed is experimentally restricted by ligation or microsphere embolization. It also occurs when the uterine caruncles of the sheep are severely reduced surgically before pregnancy. It is interesting, however, that although there are fewer cotyledons in subsequent pregnancies they are significantly larger, suggesting some fetal influence upon the growth of the cotyledonous mass. Exposure of pregnant sheep to heat also leads to significant reduction in fetal size.

In mice, an explanation of immunological influences upon placental growth has been sought by crossing different strains and comparing the results with placental development of inbred strains but so far the results have been conflicting. Blastocyst transfer, the removal of some fetuses in litter-bearing species, the introduction of teratogens, and the induction of infectious diseases are other methods that have been employed to answer specific questions. Severe maternal nutritional deprivation is associated with pronounced reduction of fetal growth. Fetal hypophysectomy, thyroidectomy, or nephrectomy are associated with stunted growth in sheep. The mechanisms of these effects remain undetermined. Any attempt to relate the results of these ablative studies to the development of the human fetus is fraught with difficulty. The human models of anencephaly or ateliotic dwarfism cannot currently be used in a comparative context because of lack of information on the intrauterine hormonal environment.

The value of many of the animal experiments performed so far is limited in that they delineate deleterious influences rather than clarify the physiological mechanisms that normally control fetal growth. Moreover, in most cases it has not been possible to draw rigorous conclusions as the insults have not been sufficiently quantitated. The extrapolation of the results to human pregnancy is further limited by marked differences in the endocrine parameters of pregnancy, and the uterine and placental structure and blood supply in the species employed. Animal studies have also not provided a model to permit investigation of severe pre-eclampsia, one of the commonest causes of human fetal growth retardation.

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[1] Wigglesworth, J. S. (1966) Fetal growth retardation, *Brit. med. Bull.* **22**, 13.

Further studies are needed in many areas. Methods must be developed in animals to assess placental perfusion characteristics (fetal and maternal) more adequately, with the ultimate goal of developing a satisfactory human placental function test.

At present our knowledge is also grossly inadequate with respect to the existence of fetal regulatory mechanisms that directly affect placental growth and transfer. Further animal studies in this area are needed.

Pathological findings in placentas of subhuman primates suggest that some species may have lesions similar to those of pre-eclampsia. Further efforts should be made to elucidate these findings by studying primate pregnancies.

At present the mechanisms that control trophoblast expansion or its endocrine performance are not understood, although some experiments suggest participation of immune mechanisms in the former. Since these relate closely to placental development, studies must be undertaken to further our knowledge in this area.

4. ROLE OF FETAL MATURATION IN THE INITIATION OF LABOUR

Despite considerable research,[1] the mechanism for the initiation of parturition in man is still not understood. However, recent investigations, stimulated by genetic and teratological observations in cattle and sheep, have demonstrated the active involvement of the fetus in determining the duration of pregnancy. They showed that ablation of the pituitary of the fetal lamb led to an indefinite prolongation of pregnancy, whereas infusion of adrenocorticotrophin (ACTH) or glucocorticoids into the fetus resulted in premature parturition. This work focused attention on the possibility that the fetal pituitary–adrenal system was involved in the initiation of parturition. This hypothesis was supported by an observed rise in plasma corticosteroid concentration in the fetus during the 7–10 days before birth. This rise is unrelated to maternal plasma corticosteroid concentration but was subsequently shown to result from an increased secretion of cortisol by the fetal adrenal gland together with an increase in cortisol-binding globulin in fetal plasma. In the rhesus monkey, ablation of the fetal pituitary gland led to a significant prolongation of gestation with marked involution of the fetal zone of the adrenal and differentiation of the adult portion.

Evidence that the fetal pituitary–adrenal system plays a similar role in the initiation of labour in man is not yet conclusive. General opinion favours the view that anencephaly with adrenal hypoplasia predisposes to

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 471.