

INTRAUTERINE GROWTH AND DEVELOPMENT

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Abstract: *Intrauterine growth in the first trimester resides in increasing the number of cells, in the second trimester, in increasing both, the number and the size, and in the third trimester, the growth in size continues but at a lower rate of cell division. In the first 28 weeks, weight reaches 1.5 kilograms and only 5 g are fats. In the last trimester, the quick acquisition of proteins and fats leads to the duplication of weight, from 1.5 to 3 kg, of which 0.5 kg (~ 16.6%) is fat. The lipid accumulation of the foetus in the third trimester (primarily conditioned by the presence of nutrients and the foetal secretion of insulin), is an important determinant of birth weight. The factors involved in the intrauterine growth are genetic, maternal environmental, nutritional (maternal and placental), of growth involved in the embryo-growth/subsequent tissue differentiation and endocrinal (maternal, placental, foetal). The growth control is nutritional, endocrinal, and paracrine.*

Cuvinte cheie: *creștere intrauterină, genetică, nutriție, endocrinologie*

Rezumat: *Creșterea intrauterină rezida în primul trimestru în creșterea numărului de celule, în al doilea, în creșterea în număr și mărime, iar în cel de-al treilea trimestru continuă creșterea în mărime însă cu o rată a diviziunii celulare mai scăzută. În primele 28 de săptămâni, greutatea atinge 1,5 kg și doar 5 g sunt grăsimi. În ultimul semestru, achiziția rapidă de proteine și grăsimi, duce la dublarea greutății, de la 1,5 la 3 kg, 0,5kg (~ 16,6%) fiind grăsimi. Acumularea lipidică a fătului în trimestrul 3 (condiționată primar de prezența de nutrienți și de secreția fetală de insulină), este un determinant important al greutății la naștere. Factori implicați în creșterea intrauterină sunt genetici, de mediu maternal, nutriționali (maternal și placentar), de creștere implicați în embriogeneză / diferențiere tisulară ulterioară și, endocrini (maternali, placentari, fetali). Controlul creșterii este nutrițional, endocrin, paracrin.*

1. Introduction

Intrauterine growth is accompanied by cell differentiation or transformation from a relatively non-specialized phenotype to cells with specific functions.

The human foetus passes through 42 successive mitotic divisions from the fertilized egg stage to the stage of new-born at term. There are only 5 more divisions needed to reach the adult age. The prenatal period (from fecundation until birth) includes the zygote stage (0-14 days), embryo stage (14 days -12 weeks), and foetus stage (12 weeks until birth).

In the first trimester, there is an increase in the number of cells, in the second trimester, a stable rate of increase in both number and size, and in the third trimester the division rate decreases, but the increase in cell size continues. Intrauterine growth retardation (IRGU) in trimester 2 and 3 may occur either by slowing the mitotic rate, or by preventing cell hypertrophy. The earlier IGRU appears, the more likely, it will be irreversible and lead to retard growth childbirth.

The growth rate in length is maximized at about 20 weeks, and in terms of weight, the growth rate is maximized at 34 weeks.

There is a difference *in length* between girls and boys, of about 0.8 cm at 30 weeks of gestation and 1 cm at 40 weeks.

In the first 28 weeks, *weight* reaches 1.5 kilograms and only 5 grams are fat. In the last quarter, by the rapid acquisition of protein and fat, the foetus doubles its weight, from 1.5 to 3

kg, 0.5 kg (~ 16.6%) being fat. A term newborn male is heavier and has less fat than females, possibly due to the effect of foetal testosterone production. The lipid accumulation of foetus in the third quarter (primarily conditioned by the presence of nutrients and the foetal secretion of insulin), is an important determinant of birth weight.

2. Factors involved in intrauterine growth

2.1 Partition of genetic and environmental factors. (1,2,3,4,5,7,10)

Prenatal growth is conditioned by *genetic, maternal, placental* and *foetal* factors. The growth controls are nutritional, endocrinal, paracrine. Mathematical models have been proposed since 1954 (9th International Congress of Genetics) regarding the partition of the genetic and environmental contribution factors in determining the birth weight. Thus, at the coarse mode, 1/3 is on genetic factors, 1/3 of environmental factors and 1/3 of unknown factors.

2.2. Genetic factors (maternal genotype, paternal genotype).(1,2,3,4,5, 7,10,11,12,13)

They are represented by genes that encode the synthesis IGF I, II or their receptors. Insulin-like growth factors (IGF I, II) have a decisive role in the development of uterine body.

Maternal genotype is responsible of the normal placental and foetal growth; the IGF II receptor gene should be maternal. The experiments conducted on mice have shown that the lower expression of IGF-II gene (maternal disomie) results

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in dwarfism.

The paternal genotype

- Father's contribution is only by foetal genotype. Although the contribution of the father on the birth weight is modest, paternal genome is essential for trophoblastic development. In the presence of two copies of the paternal genome, trophoblastic tumours may occur.
- Genetic experiments on mice have shown that, for the normal placental and foetal growth, IGF-II gene has to be paternal. On mice, the super-expression of IGF-II gene (paternal disomie) causes a foetal overgrowth. In humans, the isopaternal inheritance of IGF-II alleles (11p15,5) is associated with *Beckwith-Wiedemann syndrome* (syndrome characterized by overgrowth and the development of tumours).

2.2. Maternal environment (1,2,3,4,5,7,9)

There is a high correlation between the weight of the parents and the weight of the newborn at birth; the correlations regarding the birth weight are high in the case of half siblings with the common mother and lost in half siblings with the common father. The evidence of the maternal factor is obvious even when the comparison is extended to first cousins.

Classical transplantation experiments with embryonic crossbreeding on horses and pigs, made for the first time by Walton and Hammond, have confirmed that this effect is likely non-genetic; for example, a small embryo transplanted in a large uterus will grow bigger than a small embryo which remains into a small uterus. Also, a large embryo transplanted in a small uterus will be smaller than in its natural environment. In conclusion, the foetus transplanted into a different uterus grows at a rate corresponding to the mother vessel.

The phenomenon by which the maternal environment affects, in a non-genomic way, the foetal growth is physiological and it is called *phenomenon of coercion*, maternal "constraint". Constraining factors include: limited capacity of the uterine circulation, the uterus and the placental bed limited support capacity of the placental function. (e.g. individual triplets weigh, on average, less than a single foetus).

2.3. Nutritional factors (maternal, placental) (1,2,3,4,5,7,9)

a) maternal nutritional factors

The minimum caloric nutritional needs for fat are 95 Kcal / kg / day, of which 40 are needed to the growth and 55 are oxidized;

The maternal metabolism needs to carry the product of conception and to prepare for the lactation. The extra caloric needs are of the order of 20 000 kcal (less than 100kcal/day), but with individual and ethnic differences among women. Basal Metabolic Rate (BMR) of the pregnant women is racially different (for example, in Europe RMB evolves differently from that of women in the Gambia).

Malnutrition was generally considered to have a relatively small effect on the foetal growth. Periods of fasting (starvation) led to a small decrease in weight at birth, when the milk intake fell below 1500 kcal/day in the third trimester. However, more subtle degrees of malnutrition may have long term consequences for growth and postnatal development. However, there are studies showing multi-generation effects (grandmother's malnutrition in the first trimester influenced mother's uterine growth, without influencing the mother's birth weight).

b) Nutritional placental factors

The placenta represents the means by which nutrients and O₂ are provided to the foetus and by which the residual products are removed; sometimes, however, the foetal growth is sacrificed for placental integrity. The placenta grows faster than

the foetus and reaches the maximum weight at 33 weeks of gestation. Alterations in the development of placental structure, in the foetal or placental arterial flow or in the properties of diffusion, the transport through the placenta, may affect its ability to provide nutrients to the foetus.

The placental gas exchange (providing oxygen and removing CO₂) takes place through passive diffusion. The major physiological determinants of O₂ supply are: the blood flow of the maternal uterus, the umbilical blood flow, the foetal and maternal haemoglobin affinities for oxygen and the diffusion placental surface. Decreasing the diffusion surface or increasing the diffusion distance (e.g. Inter-villous deposition of fibrin) leads to reducing the oxygen diffusion capacity taken overall, which may restrict the foetal growth.

The addition of *amino acids* is more than necessary for the foetal protein synthesis, the remainder being oxidized, transaminated, and stored as fat. The transport of amino acids is active. The netto amino acid intake provides more than half of the fetal carbon amount and more than one and a half of the amount of nitrogen necessary to the normal growth. The foetus' capacity to oxidize the excess foetal amino acids seems to be developed during the early gestation. The placenta and foetus circulate the amino acids, metabolize them and produce ammonia; the placental ammonia passes both to the maternal and umbilical circulation. Not all amino acids contribute equally to the excess of urea. Glycine histidine, lysine, asparagine/aspartate and glutamine/glutamate, however, are all taken in similar amounts and, any deficiency in the milk intake is harmful to the foetal growth.

The transport of *fatty acids* is passive. The bigger the carbon atom contents of the lipid molecules, the higher their contribution of foetal metabolism. Since the foetal fatty acid composition varies along with the maternal diet, it is unlikely that the placenta exercises a selection in the delivery of lipids.

The *glucose* transport is completed by diffusion, a facility mediated by specific transporter proteins (GLUT1, GLUT3). The flux of glucose through the placenta is bidirectional. Studies on glucose carriers (GLUT 1, GLUT 3) showed that their function and controlling were unchanged in conditions associated with IUGR. The placenta can consume 30-50% of the total glucose and oxygen quantity for its own metabolism.

The late foetal development requires an adequate intake of *trace elements* and *vitamins*. *Mineral elements* such as calcium, phosphorus and iron reach the foetal level by active transport. At term, the foetal blood levels of these elements exceed those of the mother. Optimal intake of zinc increases with ~ 250g birth weight, and the skull circumference with 0.7 cm.

The fat soluble vitamins (A, D, E, K) cross the placenta by diffusion, and the foetal levels are less or equal than the maternal ones; *water soluble vitamins B, C* cross the placenta by active transport, and the foetal levels are higher than the maternal ones.

The high metabolic rate of the placenta affects the amount of nutrients that go to the foetus. The placental utilization of nutrients is dependent on foetal status. The placental alterations can have major effects regarding the foetal nutrient supply. The placental metabolic changes and modifications related to the transport capacity, linked to the growth result in the modification of the foetal diet throughout gestation.

The foetal metabolic rate constant at different concentrations of glucose indicates that there are important alternative substrates. Foetus can be catabolic to ensure its survival, releasing amino acids to the placenta for the

gluconeogenesis or for the direct oxidation. Thus, growth is compromised in order to ensure the placental functionality. If the foetus becomes catabolic during the last trimester, the loss of foetal protein exceeds those of fat, causing weight loss in the foetus and is ultrasound detectable.

2.4. Growth factors involved in further embryogenesis/tissue differentiation (1,2,3,4,5,7,9)

Factor	Source	Foetal effects
TGF (transforming growth factor)	Multiple tissues	Regulates cell division, differentiation and deposition of extra cellular matrix
FGF	fibroblasts	Regulates extra cellular division, angiogenesis
PDGF	platelets other tissues	Necessary for cellular replication
EGF	Multiple tissues	Regulates epithelial cell division
NGF	Multiple tissues, including the placenta	Neural development

2.5. Maternal, placental, foetal endocrine factors (1,2,3,6,7,8,9,11,12,13,14):

Maternal endocrine factors are represented by factors IGF-1, synthesized under the action of Placental Lactogen (hPLCS - A, B) in the first part of gestation, and the growth hormone GH (hGH-V). They have an anabolic role by increasing the concentrations of glucose and fatty acids. The glucose is used preferentially by the foetal-placental unit, and the free fatty acids are used as nutritional substrate by the mother.

Placental endocrine factors are the hormones with a progestagen role (inhibins, activins, progesterone, estrogen, hormone chorionic gonadotropin-hCG) or the role of fetal-placental growth and the hyperglycaemia maternal (Placental Lactogen-hPLCS-A, B and the growth hormone variant hGH-V).

The foetal endocrine factors are primarily insulin-like growth factors (IGF-1,2), thyroid hormones, GH's foetal insulin, steroid hormones.

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