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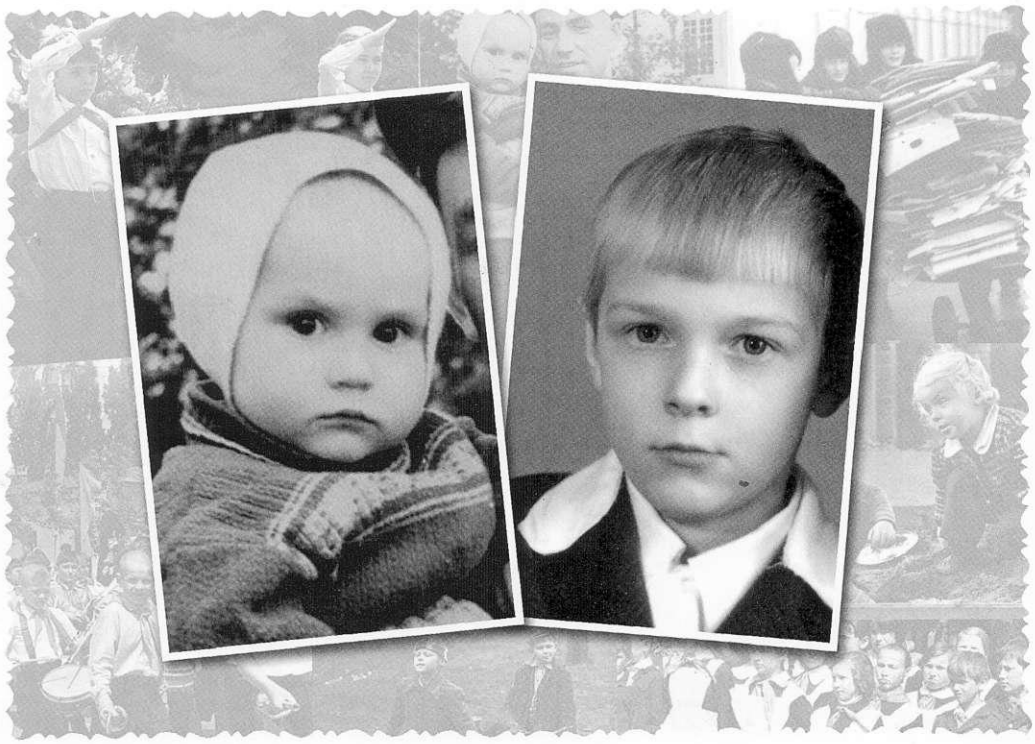

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ГИ ПРОФЕССИОНАЛЬНЫЕ ИЗДАНИЯ

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The physiology and regulation of human fetal growth (part I)

Физиология и регулирование развития плода (часть 1)

Abstract

The article "Physiology and regulation of development of fetus and newborn child (Part I)" of Sofvat Hassan and Beketova G. modern data on the physiological aspects of regulatory development of the fetus and newborn child are presented. The most recent data on the effect of the maternal genome and environment, state of uterine blood flow, hypoxia, chronic diseases, maternal smoking, role of the placenta in fetal development are discussed. The data on metabolic and endocrine functions of the placenta are presented as well. Questions regarding endocrine regulation of fetus and newborn child will be discussed in the second part of the article.
Keywords: fetus, newborn, growth, regulation, placenta.

Резюме

В статье «Физиология и регулирование развития плода (часть I)» Софват Хассана, Бекетовой Г.В. представлены современные данные, касающиеся физиологических аспектов регулирования развития плода. Обсуждаются наиболее современные данные о влиянии материнского генома и окружающей среды, состояния маточного кровотока, гипоксии, хронических заболеваний, курения матери, роли плаценты в развитии плода. Представлены данные о метаболической и эндокринной функциях плаценты. Вопросы, касающиеся эндокринной регуляции развития плода и новорожденного ребенка, будут рассмотрены во второй части статьи.
Ключевые слова: плод, новорожденный ребенок, развитие, регуляция, плацента.

The environment in which the fetus develops plays an important role in its growth and development as it is critical for fetal survival and long term health [215]. The regulation of normal human fetal growth involves many multidirectional interactions between the mother, placenta, and fetus. The mother supplies nutrients and oxygen to the fetus via placenta. The fetus influences the provision of maternal nutrients via the placental production of hormones that regulate maternal metabolism. The placenta is the site of exchange between mother and fetus and regulates fetal growth via production and metabolism of growth-regulating hormones such as IGFs and glucocorticoids. Adequate trophoblast invasion in early pregnancy and increased utero-placental blood flow ensure sufficient growth of the uterus,

placenta, and fetus. The placenta may respond to fetal endocrine signals to increase transport of maternal nutrients by growth of the placenta, by activation of transport systems, and by production of placental hormones to influence maternal physiology and even behavior (Endocrine Reviews, 2006).

The Role of Mother in Fetal Growth and Development

The maternal genome and the maternal environment: Normal fetal growth involves an increase in cell number during embryonic and fetal development, followed by an increase in cell size, which become dominant after 32 weeks gestation. Fetal growth and development are influenced by genetic as well as environmental factors. Maternal genes have an important specific influence over fetal growth [221]. In particular, maternal height, which represents uterine capacity and the potential for growth, is a major determinant of fetal size. Although, the birth weights are similar and correlate among siblings, it is known that environmental influences are also important in determining growth. This is demonstrated by the fact that birth weights are more closely related in half-siblings with the same mother than in those with the same father [103]. In the study of pregnancies involving ovum donation, Brooks et al. [36] found that the only factors contributing to birth weight were gestational age and the recipient mother's weight, whereas the weight of the donor mothers was not related to birth weight. These studies indicate that the uterine environment is a key determinant of fetal growth [36]. A variety of maternal and uteroplacental factors limit the growth of the fetus. Maternal constraints refer to the limited capacity of the uterus to support fetal growth and are important to limit fetal overgrowth and the subsequent dystocia, to ensure the capacity of mother for future successful pregnancies. Maternal constraint may be supply limited, by maternal size or nutrient availability, or may be demand driven as in the case of multiple pregnancies [104].

Maternal nutrient intake: The mother is the supplier of oxygen and essential nutrients to the fetus via the placenta. Maternal diet, caloric intake and metabolic function each have an important role to play in supplying nutrients to the fetus. In addition, alterations in maternal metabolism in response to hormonal signals ensure a redirection of required nutrients to the placenta and mammary gland [222]. Increased caloric intake is necessary during the second and third trimesters to cope with most fetal and placental growth [222]. Protein intake may be particularly important, and whereas some studies found a relationship between low protein intake in late pregnancy and reduced birth weight [105], others found no effect of protein supplementation on fetal growth in undernourished mothers [45]. Nonetheless supplementation of calories or specific vitamins to undernourished women may increase birth weight in situations of acute and or chronic starvation [45], for example, folic acid, iron and vitamin A supplementation to pregnant women in Nepal resulted in an increase in mean birth weight of 37 g and a 16% reduction in the rate of low birth weight compared with pregnant women given vitamin A alone. However, multiple micronutrient supplementation with folic acid, zinc, iron, vitamin A and 10 other micronutrients was not of additional benefit compared with folic acid and iron, suggesting that iron deficiency may be an important cause of reduced fetal growth. A Cochrane systematic review of six randomized controlled trials found that balanced protein-energy supplemen-

tation was able to reduce the risk of small for gestational age (SGA) neonates by approximately 30% [164]. Glucose is an important nutrient in the control of fetal growth. Studies of diabetic women have shown that low blood glucose levels during pregnancy as a result of excessively tight glycemic control leads to a greater incidence of small for gestational age (SGA) neonates whereas having high blood glucose levels contributes to a high incidence of macrosomia [170]. Different protein sources may also have specific influences on fetal growth due to their amino acids and micronutrients composition. There is correlation between dietary protein intake and placental weight & femur length [105, 52].

Maternal uterine artery blood flow: Increased uterine blood flow is essential to meet metabolic demand from the growing uterus as well as the placenta and the fetus [161]. The maternal blood volume and cardiac output increase by approximately 40% during pregnancy [229], and the total uteroplacental blood flow represents 25% of cardiac output [161, 266] found that uterine artery volume flow rate increased by more than 3-fold during pregnancy, partly influenced by an increase artery diameter and reduced resistance to flow [266]. In addition to increased uterine blood flow during normal pregnancy, the development of new blood vessels also occurs in the uterus, possibly promoted by the placental hormones, human chorionic gonadotropins (hCG) and IGF2 [300]. Using Doppler assessment of the uterine arteries at 23 weeks gestation, Albaiges et al. [4] identified that uterine artery blood flow resistance was associated with an increased risk of subsequent small for gestational age (SGA) neonates [4].

Influences on Maternal Development during Pregnancy

Maternal hypoxia. Maternal hypoxia influences fetal growth, and its effect is independent of socioeconomic status, prematurely, maternal smoking, pregnancy-induced hypertension and parity [146].

Maternal inflammatory diseases: The presence of maternal inflammatory disease may contribute to reduced fetal growth. We have investigated the effect of maternal asthma on fetal growth and placental function. Previous epidemiological studies have linked maternal asthma with an increased risk of low birth weight [174]; however, the mechanisms are poorly understood.

Maternal smoking and drug use: Maternal cigarette smoking is associated with reduced birth weight, and early reports suggested a doubling of the rate of low birth weight in smokers compared with nonsmokers and a dose-dependent effect with increasing number of cigarettes smoked [180]. More recent studies demonstrate a 3.5 fold increased risk of small for gestational age (SGA) neonates in women who smoke during pregnancy. [13] with a greater effect on low birth weight with increasing maternal age [228]. Maternal smoking affects the entire rang of birth weights shifting the birth weight distribution curve to the left [228]. The mechanism of the effect of maternal smoking relates to both the higher levels of carbon monoxide in maternal blood that cross the placenta to the fetus, leading to fetal tissue hypoxemia and the vasoconstrictive effects of nicotine [206]. In addition to, there may be an interaction between maternal smoking and nutritional intake, which adversely affects fetal growth. Women who smoke have different diets from non-smokers due to suppression of appetite by smoking. Components of cigarette smoke have effects on amino acid transport from the mother to

fetus. In vitro, nicotine has been demonstrated to reduce activity of the major transporter of the microvillus membrane, sodium-dependent system A, in human placental slices suggesting an independent effect of nicotine associated with intrauterine growth retardation (IUGR) [85]. Such changes in amino acid transport are significant for the development of intrauterine growth retardation (IUGR), due to the small difference between the placental capacity to transport amino acids and fetal demand [219].

Role of placenta in fetal growth and development: Development of placenta is a highly regulated process that is essential for normal fetal growth and development, and for maintenance of a healthy pregnancy. The placenta fulfills several critical rules as the interface between mother and fetus; preventing rejection of the fetal allograft; adequate trophoblast invasion; an increase in utero-placental blood flow during gestation; transporting and metabolizing nutrients such as glucose and amino acids from mother to fetus and production and transfer of growth regulating hormones and peptide [276]. The placenta receives and transmits endocrine signals between the mother and fetus. The total placental surface area for exchange is llm2 at term [3; 158]. In fetal growth restriction, both the placental villous surface area and placental volume are decreased [158]. Adequate placental growth is essential for adequate fetal growth. Small for gestational age (SGA) neonates have significantly reduced placental weights compared with appropriately grown neonates of the same birth weight [128].

Function of Placenta

Trophoblast invasion and increased uteroplacental blood flow

Adequate trophoblast invasion is required to sustain fetal growth, when the blastocyte adheres to the uterus, fetal trophoblast cells differentiate into villous and extravillous cells [276; 229]. Migration and invasion of extravillous cyto-trophoblast into the maternal uterine epithelium are processes that are essential for increased uteroplacental blood flow as pregnancy progresses [229]. Maternal uterine spiral arteries are transformed into larger, low resistance vessels, capable of transporting the increased maternal blood to the placenta [182]. The absence of trophoblast – induced changes in decidual or myometrial segments of spiral arteries is a feature of some pregnancies complicated by fetal growth restriction [161]. The cyncytiotrophoblast cell layer, which is differentiated from cyto-trophoblast cells, is the site where hormones such as estrogen, progesterone, hCG, placental lactogen, and placental growth hormone are produced to maintain the pregnancy [104]. Increased blood flow during pregnancy increases the flow of nutrients from the mother to the fetus. Utero-placental blood flow was shown to be reduced by up to 50% in women with preeclampsia. Also there is a decrease in number and surface area of terminal villi in intrauterine growth restriction (IUGR), representing a malfunction of vascularization in these pregnancies [300]. Many studies suggest the importance of trophoblast invasion and changes in Utero-placental and umbilical blood flow for maintaining appropriate fetal growth through the supply of oxygen and nutrients [13; 84; 18; 68].

Transport of nutrient and specific substance across the placenta

The placenta is a metabolically active organ that extracts 40–60% of the total glucose and oxygen supplied by the uterine circulation [22]. The

remaining nutrients and metabolites are transferred across the placenta to the fetus by passive diffusion, facilitated diffusion, active transport and endocytosis or exocytosis [247]. Transport by passive diffusion (of oxygen, carbon dioxide, and urea) is limited by the placental exchange area and blood flow. Facilitated diffusion (of glucose and lactate) involves transfer down a concentration gradient by a carrier molecule, without a requirement for additional energy. Active transport requires both carrier proteins and the input of additional energy [22]. Placental transfer increases as the fetal growth rate increases [247].

Respiratory gas exchange: Both oxygen and carbon dioxide are lipophilic molecules which will cross the placenta by simple diffusion. The placental membranes are highly permeable to O2 and CO2 thus blood flow is the rate limiting step for exchange of the respiratory gases across this tissue. The partial pressure and the difference between maternal and fetal hemoglobin affinity for O2 are two important factors that determine rate of exchange [43].

Amino acid transport: Amino acids are essential for fetal growth as they are the components of protein synthesis. Additionally, their degradation and interconversion to intermediate substrates gives rise to synthesis of either glucose or ketone bodies. The placenta plays a critical role in the delivery of amino acids to the fetus. Transfer involves three fundamental steps: uptake from the maternal circulation across the micro-villous membrane, transport through the trophoblast cytoplasm, and transport across the basal membrane in to the umbilical circulation [227]. Transport systems within the trophoblast can be either sodium-dependent or sodium-independent, and differ based on their ionic substrates [227; 144]. Amino acids may also be metabolized and processed by the placenta. For example, leucine is deaminated in the placenta and the deaminated product and leucine itself are both transferred to the fetus [177]. In fetal growth restriction there are alterations in amino acid transport by the placenta and uptake by the fetus. The fetus may influence the expression of placental amino acid transporters in response to a slowing of fetal growth. Studies in transgenic mice lacking the PO transcript of the IGF-II gene found that whereas there was a decrease in a passive diffusion of nutrients in association with reduced growth, there was an up-regulation of active amino acid transport, possibly as a compensatory mechanism to attempt to improve fetal growth, the fetus may signal to the mother, through the placenta, that more nutrients are required in the case of poor growth.

Glucose transport: Glucose is the main source of energy for the human fetus and placenta as the glucose is the primary substrate for fetal oxidative metabolism, thus its efficient transfer across the placenta is essential for normal fetal growth and development. The placenta itself is not capable of producing appreciable amounts of glucose until late in gestation [276] and the fetus produces minimal amounts of glucose, thereby requiring glucose transport from the mother for glycogen synthesis. The process of glucose transport from the mother is carried out by facilitated diffusion using transporters found on the maternal and fetal sides of the trophoblast [188]. Glucose transporter 1 is found in abundance in the micro-villous membrane of the syncytio-trophoblast at levels three times higher than the basal membrane [142; 21]. In normal pregnancy; there is a state of insulin resistance so as to increase glucose availability for the fetus. Insulin resis-

tance is exacerbated in diabetic pregnancy, where the mother may become hyperglycemic, leading to fetal hyperglycemia. As a result of fetal hyperglycemia, there is increased production of insulin, IGF-1, and leptin, resulting in stimulation of fetoplacental growth [203]. Hypoglycemia in small for gestational age (SGA) fetuses may be related to reduced supply and transfer of glucose across the placenta [72]. In a perfusion study, baseline glucose consumption was 2-folds higher in preterm intrauterine growth restriction (IUGR) placenta compared with normally grown preterm placenta, suggesting that placental consumption of glucose may contribute to alterations in maternal-fetal concentration differences in glucose. However, there was no changes in glucose transfer to the fetal side of the placenta [4], confirming previous work showing no alteration in glucose transporter expression or activity in intrauterine growth restriction (IUGR) placenta [142]. Another study found that the maternal-fetal glucose concentration gradient was increased in relation to the clinical severity of intrauterine growth restriction (IUGR), possibly representing an adaptation to maintain glucose uptake across the placenta [188].

Fatty acid transport: Fatty acid are essential for fetal development, both as an energy source and also as a precursor for several important bioactive compounds, such as prostaglandins and thromboxane. In the third trimester , fatty acids are required for changes in fetal tissue composition ,particularly that of the brain and adipose tissue [276].

The placenta has a considerable capacity for fat uptake and transport of fatty acids. Uptake involves the breakdown of triglycerides (from maternal adipose tissue) to free fatty acids and glycerol and re-esterification with intracellular generated glycerol phosphate and this conversion is mediated by lipase activity [276]. Free fatty acids may be transported across the placenta via passive diffusion as well as by fatty acid binding proteins and fatty acid transfer proteins in the microvillus and basal membranes [114; 97]. The essential fatty acid, linoleic acid, was found to be significantly higher in intrauterine growth restriction (IUGR) placenta compared with those from appropriately grown fetuses [218], which may have implication for fetal brain development [60]. The activity of lipoprotein lipase, and triglyceride hydrolase in microvillous membrane, was recently found to be reduced in preterm, intrauterine growth restriction (IUGR) samples compared with gestational age-matched controls [184].

Metabolic and Endocrine function. The metabolic and endocrine functions of the placenta are a complex network of substrate/hormone production and metabolism that must be tightly controlled to ensure normal fetal growth and development, and maintenance of a healthy pregnancy [276].

Metabolic functions: The placenta is capable of synthesizing glycogen and cholesterol, which are energy source to the developing fetus. Additionally, cholesterol is an important precursor for hormone production by the feto-placental unit.

Glycogen synthesis. The placenta is capable of synthesizing appreciable amounts of glycogen, which it stores as an energy reserve. The uptake of glucose from the maternal circulation is a rate limiting step in this process, which involves a series of enzymes and regulators. Of particular importance is the enzyme glycogenic, which is co-expressed with the high affinity

GLUT-3 transporter in the endothelium, basal deciduas, and invading extra villous trophoblast of the human placenta [115].

Cholesterol synthesis. The demands for cholesterol in the fetus are high and, in early pregnancy, maternal cholesterol contributes substantially to this requirement. In late gestation, the fetus' itself synthesizes cholesterol from placental stores of fatty acids established from maternal body fat accumulation in early pregnancy. Placental cholesterol is an important precursor for placental production of progesterone and estrogens [130].

Protein metabolism. Protein metabolism in the placenta is largely governed by the demands of growth throughout gestation. At week 10, placental protein production is approximately 1.5 gram per day, but by term this figure rises to 7.5 gram daily [241].

Lactate metabolism: Lactate, a waste product of metabolism, is produced in large quantities by the placenta and therefore needs to be efficiently removed. L-lactate transporters are active on the microvillous membrane of human placenta and are present on the basal membrane [241].

Endocrine functions: During human pregnancy, the placenta is an important endocrine organ. The placenta is not innervated; hence any communication between the mother, and the fetus must involve humoral agents. The signaling molecules secreted by the placenta can act locally through paracrine and autocrine regulation. The placenta also acts as an important endocrine organ and is responsible for the release of hormones into both the fetal and maternal circulation. The main site of production of the placental hormones is the trophoblast of the chorionic villi [276].

ЛИТЕРАТУРА

1. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J & Osgood D (2003): IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med, 349: 2211-2222.
2. Adashi, EY, Hsueli, AJ, Yen, SS (1981): Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells. Endocrinology; 108: 1441.
3. Aherne W (1975): Morphometry In: Gruenwald P, ed. The placenta and its maternal supply line. Baltimore: University Park Press; 80-97.
4. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH (2000): One-stage screening for pregnancy complication by color Doppler assessment of the uterine arteries at 23 weeks gestation. Obstet Gynecol, 96: 559-564.
5. Albiston AL, Obeyesekere VR, Smith RE, Krozowski ZS (1994): Cloning and tissue distribution of the human 11 p-hydroxysteroid dehydrogenase type 2 enzyme. Mol Cell Endocrinol, 105: Rl 1-R17.
6. Ariyasu, H, Takaya, K, Hosoda H, Iwakura H, Ebihara K, Mori K (2002): Delayed short- term secretory regulation of ghrelin in obese animals: evidenced by a specific RIA for the active form of ghrelin. Endocrinology; 143: 3341-3350.
7. Ariyasu, H, Takaya, K, Tagami, T (2001): Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin- like immuno-reactivity levels in humans. J Clin Endocrinol Metab, 86: 4753.
8. Arslanian, SA, Lewy, V, Danadian, K, Saad, R (2002): Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab; 87: 1555.
9. Asakawa A, Inuti A, Fujimiya M, Sakamaki R, Shinfuku N, Ueta Y (2005): Stomach regulates energy balance via acylated ghrelin and deacyl ghrelin. Gut; 54: 18-24.
10. Asakawa A, Inuti A, Kaga T, Yuzuriha H, Nagata T, Ueno N (2001): Ghrelin is appetite- stimulatory signal from stomach with structural resemblance to motilin. Gastro-enterology; 120:337-345.
11. Babenko AP, Polak M, Cave H (2006): Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med; 355: 456.
12. Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonissoni S, Fubini A (2002): Ghrelin and deacyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI3-Kinase /AKT. J Cell Biol., 159: 1029-1037.
13. Bamberg C, Kalache KD (2004): Prenatal diagnosis of fetal growth restriction. Semin Fetal Neonatal Med, 9: 387-394.
14. Bang P, Westgren M, Schwander J, Blum WF, Rosenfeld RG & Stangenberg M (1994): Ontogeny of insulin-like growth factor-binding protein-1,-2 and 3: quantitative measurements by radioimmunoassay in human fetal serum. Pediatr Res, 36: 528-536.
15. Banks BA, Cnaan A, Morgan MA, Parer JT, Merrill JD, Ballard PL, Ballard RA (1999): Multiple courses of antenatal corticosteroids and outcome of premature neonates. North American Thyrotropin-Releasirig Hormone Study Group. Am J Obstet Gynecol, 181: 709-717.
16. Banks WA, Clever CM and Farrell CL (2000): Partial saturation and regional variation in the blood-to- brain of leptin in normal weight mice. AmJPhysiol;278:E1158-E 1165.
17. Banks WA, Tschop M, Robinson SM, and Heiman ML (2002): Extent and direction of ghrelin transport across the blood brain barrier is determined by its unique primary structure. J Pharmacol Exp Ther; 302: 822-827.

18. Barbera A, Galan HL, Ferrazzi E, Rigano S, Jozwik M, Battaglia FC, Pardi G (1999): Relationship of umbilical vein blood flow to growth parameters in the human fetus. Am J Obstet Gynecol, 181: 174-179.
19. Barnard, R, Waters, MJ (1997): The serum growth hormone binding protein: Pregnant with possibilities. J Endocrinol; 153: 1.
20. Barr HS, Rutherford SE (1998): classification of intrauterine growth retardation. Semin Perinatol, 12: 2-10.
21. Barros LF, Yudilevich DL, Jarvis SM, Beaumont N, Baldwin SA (1995): Quantation and immunolocalization of glucose transporters in the human placenta. Placenta, 16: 623-633.
22. Bauer MK, Harding JE, Bassett NS, Breier BH, Oliver MH, Gallaher BH, Evans PC, Woodall SM, Gluckman PD (1998): Fetal growth and placental function. Mol Cell Endocrinal, 140: 115-120.
23. Beaconsfield, P, Birdwood, G, Beaconsfield, R (1980): The placenta. Sci Am 1980; 243: 94.
24. Bedendi I, Alloatti G, Marcantoni A, Malan D, Catapano F, Ghe C (2003): Cardiac effects of ghrelin and its endogenous derivatives des-octanoyl ghrelin and des-Gln-14-ghrelin.Eur J Pharmacol; 476: 87-95.
25. Bellon S, Rapa A, Vivenza D, Castellino N, Petri A, Bellone J (2002): Circulating ghrelin levels as function of gender , pubertal status and adiposity in childhood. J Endocrinol Invest; 25 (5): RC 13-5.
26. Bellone S, Rapa A, Vivenza D, Vercellotti A, Petri A, Radetti G, Bellone J, Broglio F, Ghigo E & Bona G (2003): Circulating ghrelin levels in newborns are not associated with gender, body weight and hormones parameters. Journal of Endocrinological investigation, 26,RC 9-11.
27. Bellone S, Rapa A, Vivenza D, Vercellotti A, Petri A, Radettit G & Bellone J (2004): Circulating ghrelin levels in newborn are positively associated with gestational age. Clin Endocrin, 60: 613-617.
28. Benediktsson R, Calder AA, Edwards CR, Seckl JR (1997): Placental 1 lp-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure . Clin Endocrinol (Oxf) 46: 161-166.
29. Bingley, PJ, Matthews, DR, Williams, AJ (1992): Loss of regular oscillatory insulin secretion in islet cell antibody positive non-diabetic subjects. Diabetologia; 35: 32.
30. Bloom SL, Sheffield JS, McIntire DD, Leveno KJ (2001): Antenatal dexamethasone and decreased birth weight . Obstet Gynecol 97: 485-490.
31. Book, CB, Dunaif, A. Selective insulin resistance in the polycystic ovarian syndrome. J Clin Endocrinol Metab 1999; 84: 3110.
32. Bowers CY, Diegues C, Ghigo E, Boghen M, Casanueva FF (1999): Growth hormone secretagogues , Amsterdam, Elsevier Science: 5-18.
33. Breier BH, Funk B and Surus A (1994): Characterization of ovine growth hormone (oGH) and ovine placental lactogen (oPL) binding to fetal and adult hepatic tissue in sheep: evidence that o GH and oPL interact with common receptor. Endocrinology; 135: 919-928.
34. Brent, GA (2000): Tissue-specific actions of thyroid hormone: insights from animal models. Rev Endocr Metab Disord; 1: 27.
35. Broglio F, Arvat E, Benso A, Gottoro C, Muccioli G, Papotti M (2001): Ghrelin , a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. J Clin Endocrinol Metab; 86: 5083-5086.
36. Brooks AA, Johnson MR, Steer PJ, Pawson ME, Abdalla HI (1995): Birth weight: nature or nurture? Early Human Development, 42: 29-35.
37. Brown RW, Champman KE, Edwards CR, Seckl JR (1993): Human placental 11 (3-hydroxysteroid dehydrogenase: evidence for and partial putrification of a distinct NAD-dependant isoform Endocrinology, 132: 2614-2621.
38. Bujalaska I, Shimojo M, Howie A, Stewart PM (1997): Human lip hydroxysteroid dehydrogenase: studies on the stably transfected isoforms and localization of the type 2 isoenzyme within renal tissue. Steroids, 62: 77-82.
39. Calles-Escandon, J, Mirza, SA, Sobel, BE, Schneider, DJ (1998): Induction of hyperinsulinemia combined with hyperglycemia and hyper-triglyceridemia increases plasminogen activator inhibitor 1 in blood in normal human subjects. Diabetes; 47: 290.
40. Cao, XY, Jiang, XM, Dou, ZH (1994): Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med; 331: 1739.
41. Cappiello V, Ronchi C, Morpurgo P, Epaminonda P, Arosio M, eck-Peccoc (2002): Circulating ghrelin levels in basal conditions and during glucose tolerance test in acromegalic patients. Eur J Endocrinol; 147(2): 189-194.
42. Carel JC, Chatelain P and Rochiccicol P (2003): in improvement adult height after growth hormone treatment in adolescent with short stature born small for gestational age : results of randomized controlled study. J Clin Endocrinol Metab; 88: 1587-1593.
43. Carter, AM (1989): Factors affecting gas transfer across the placenta and the oxygen supply to the fetus. J Dev Physiol; 12-305.
44. Caspi E, Schreyer P, Weinraub Z, Bukovsky I, Tamir I (1975): Changes in aminotic fluid lecithin-sphingomyelin ratio following maternal dexthamethasone administration. Am J Obstet Gynecol, 122: 327-331.
45. Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, Whitehead RG (1997): Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomized controlled trail. Br Med J, 315: 786-790.
46. Challis DE, Pfarrer CD, Ritchie JW, Koren G, Adamson SL (2000): Glucose metabolism is elevated and vascular resistance and maternofetal transfer is normal in perfused placental cotyledons from severely growth-restricted fetuses. Pediatr Res, 47: 309-315.
47. Challis JR, Sloboda D and Matthews SC (2001): The fetal placental hypothalamic-pituitary-adrenal axis, parturition and postnatal health. Mol Cell Endocrinol, 185: 135-144.
48. Chang SC OBrien KO, Nathonson MS, Caulfield LE, Mancini J, Witter FR (2003): Fetal femur length is influenced by maternal dairy intake in pregnant African American adolescents. Am J Clin. Nutr. 77: 1248-1254.
49. Chanoine J P, Yeung LPK, Wong A.C.K, & Birmingham CL (2002): Immunoreactive ghrelin in human cord blood: relation to anthropometry, leptin and growth hormone. Journal of Pediatric Gastroenterology & Nutrition, 35: 282-286.
50. Charnock-Jones, DS, Sharkey, AM, Boocock, CA (1994): Vascular endothelial growth factor receptor localization and activation in human trophoblast and choriocarcinoma cells. Biol Reprod; 51: 524.
51. Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EG (2004): Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP). Endocrinology; 145: 2607-2612.
52. Cheng SY (2005): Thyroid hormone receptor mutations and disease: beyond thyroid hormone resistance. Trends Endocrinol Metab; 16: 176.
53. Chernausek SD, Dickson BA, Smith EP (1991): Suppression of insulin-like growth factor induced growth retardation. Am J Physiol; 260: 416-21.
54. Chidakel, A, Mentuccia, D, Celi, FS (2005): Peripheral metabolism of thyroid hormone and glucose homeostasis. Thyroid; 15: 899.
55. Chin SO, Brodsky NL, Bhandari V (2003): Antenatal steroid use is associated with increased gastroesophageal reflux in neonates. Am J Perinatol, 20:205-213.
56. Chin-Chance C, Polnosky KS, and Schoeller DA (2000): Twenty-four-hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. J Clin. Endocrinol Metab, 85: 2685-91.
57. Cortelazzi D, Capiello V, Morpurgo P S, Ronzoni S, Nobile De Santis M S, Cetin I, Beck-Peccoz P & Spada A (2003): Circulating levels of ghrelin in human fetuses. European Journal of Endocrinology, 149: 111-116.
58. Coulter CL, Han VK (1996): Expression of insulin-like growth factor-II and IGF-binding protein-1 mRNAs in term rhesus monkey placenta: comparison with human placenta. Horm Res, 45: 167-171.
59. Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL (2003): The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis; Neuron; 37: 649-661.
60. Crawford MA, Costeloe K, Ghebremeskel K, Phylactos A, Skirvin L, Stacey F (1997): Are deficits of arachidonic and docosa-hexaenoic responsible for the neural and vascular complications of preterm babies? Am J Clin Nutr, 66: 1032S-1041 S.
61. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, and Weigle DS (2001): A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes; 50: 1714-1719.
62. Cummings, DE, Foster-Schubert, KE, Overduin, J (2005): Ghrelin and energy balance: focus on current controversies. Curr Drug Targets; 6: 153.
63. Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T (2000): Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology; 141: 4255-4261.
64. Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Matsuo H (2002): The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. Gastroentrology, 123: 1120-1128.
65. David K McCiilloch, Paul Robertson, Jean E Mulder, David M Nathan, Joseph I Wolfsdorf (2007): Insulin secretion and pancreatic beta-cell function, Up To Date Online.

66. 66.de-Graff G, AM-Smeets P, Stafleu A, FG Hendriks H (2004): Biomarkers of satiation and satiety; American Journal of Clinical Nutrition; 79: 946-961.
67. Del Giudice, ME, Fantus, 1G, Ezzat, S (1998): Insulin and related factors in premenopausal breast cancer risk. Breast Cancer Res Treat; 47: 111.
68. Di Naro E, Raio L, Ghezzi F, Franchi M, Romano F, Addario VD (2002): Longitudinal umbilical vein blood flow changes in normal and growth-retarded fetuses. Acta Obstet Gynecol Scand, 81: 527-533.
69. Dixit VD, Schaffer EM, Pyle RS (2004): Ghrelin inhibits leptin- and activation-induced proinfiammatory cytokine expression by human monocytes and T cells. J Clin Invest; 114: 57.
70. Drazen DL, Vahl TP, D'Alessio DA (2006): Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. Endo-crinology; 147: 23.
71. Driver PM, Rauz S, Walker EA, Hewison M, Kilby MD, Stewart PM (2003): Characterization of the human trophoblast as a mineralocorticoid-target tissue. Mol Hum Reprod, 9: 793-798.
72. Econsmides DL, Nicolaides KH, Gahl WA, Bernardini I, Evans MI (1989): Plasma amino acids in appropriate- and small- for gestational-age fetuses. Am J Obstet Gynecol, 161: 1219-1227.
73. Edgerton, DS, Lautz, M, Scott, M (2006): Insulin's direct effects on the liver dominate the control of hepatic glucose production. J Clin Invest; 116: 521.
74. Efstratiadis A (1998): Genetics of mouse growth. International Journal of Developmental Biology, 42: 955-976.
75. Eggenschwiler J, Ludwig T, Fisher P, Leighton PA, Tilghman SM, Efstratiadis A (1997): Mouse mutant embryos over expressing IGF-II exhibit phenotypic features of Beckman- Wiedeman and Simpson-Golobi-Behmel syndromes. Genes and Development, 11:3128-3142.
76. Enoksson, S, Degerman, E, Hagstrom-Toft, E (1998): Various phosphodiesterase subtypes mediate the in vivo antilipolytic effect of insulin on adipose tissue and skeletal muscle in man. Diabetologia; 41: 560.
77. Eugster, EA, Pescovitz, OH (2003): New revelations about the role of STATs in stature. N Engl J Med; 349: 1110.
78. Eva L, Akos V, Kalaman A K, Tames C, Maria S, Istvan S (2008): Ghrelin and acyl ghrelin in preterm infants and maternal blood: relationship with endocrine and anthropometric measures, European Journal Endocrinology, 158:27-33.
79. Evan-Brion D, Porquet E, Thernod P (1994): Vitamin A deficiency and nocturnal growth hormone secretion in short children. Lancet; 343: 87-8.
80. Fang J, Furesz TC, Lurent RS, Smith CH, Fant ME (1997): Polarization of insulin-like growth factor receptors on the human syncytiotrophoblast. Pediatr Res, 41: 258-265.
81. Fang J, Fursez TC, Smith CH & Fant ME (1999): IGF binding protein-1 is associated with the fetal-facing basal surface of the syncytotrophobast in the human placenta. Growth Hormone IGF Res, 9: 438-444.
82. Farese RV Jr, Yost TJ, Eckel RH (1991): Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. Metabolism; 40: 214.
83. Farquhar J, Heiman M, Wong A, Wach R, Chessex P, Chanoine JP (2003): Elevated umbilical cord ghrelin concentrations in small for gestational age neonates. J of Clin Endocrin and Metab, 88: 4324-4327.
84. Ferrazzi E, Rigano S, Bozzo M, Bellotti M, Ciovannini N, Calan H, Battaglia FC (2000): Umbilical vein blood flow in growth restricted fetuses. Ultrasound Obstet Gynecol, 16: 432-438.
85. Fisher SE, Atkinson M, Van Thiel DH (1984): Selective fetal malnutrition: the effect of nicotine, ethanol, and acetaldehyde upon in vitro uptake of a-aminoisobutyric acid by human term placental villous slices. Dev Pharmacol Ther, 7: 229-238.
86. Flakoll PJ, Kulaylat M, Frexes-Steed M (1989): Amino acids augment insulin's suppression of whole body proteolysis. Am J Physiol; 257: E839.
87. Fowden AL (2003): The insulin-like growth factors and feto-placental growth. Placenta; 24: 803-12.
88. Fowden AL, Forhead AJ (2004): Endocrine mechanisms of intrauterine programming. Reproduction; 127: 515-26.
89. Fowden AL, Hill DT (2001): Intrauterine programming of the endocrine pancreas. British Medical Bulletin; 60: 123-42.
90. Fowden AL, Li J, Forhead AJ (1998): Glucocorticoids and the preparation for life after birth: are there are long term consequences of the life insurance?
91. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP (1999): Repeated antenatal corticosteroids: size at birth and subsequent development. Am J Obstet Gynecol 180: 709-717.
92. Friedman JM, Halaas JL (1998): Leptin and regulation of body weight in mammals. Nature; 395: 763-770.
93. Fujino K, Inuti A, Asakawa A, Kihara N, Fujimura, M and Fujimiya M (2003): Ghrelin mduces fasted motor activity of the gastrointestinal tract in conscious fed rats. J Physiol; 550: 227-240.
94. Fukushima, N, Hanada, R, Teranishi, H (2005): Ghrelin directly regulates bone formation. J Bone Miner Res; 20: 790.
95. Gardner RL, Squire S, Zainan S, Hills S, Graham CF (1999): Insulin-like growth factor-2 regulation of conceptus composition: effects of the trophectoderm and inner cell mass genotype in the mouse. Biology of Reproduction, 60, 190-195.
96. Gargosky SE, Owens PC, Walton PE, Pfaffle R, Raile K, Seidel B, Smith RJ and Chernausek SD (1991): Intrauterine growth retardation (IUGR) study group; Most of the circulating insulin-like growth factors-I and-II are present in the 150 kDa complex during human pregnancy. J Endocrinol, 131: 491-497.
97. Garnica AD, Chan WY (1996): The role of the placenta in fetal nutrition and growth. J Am Coll Nutr, 15: 206-222.
98. Germain-Lee EL, Janicot M, Lammers R, Ullrich A, Casella SJ (1992): Expression of a type I insulin-like growth factor receptor with low affinity for insulin-like growth factor II. Biochem J, 281: 413-417.
99. Gitau R, Cameron A, Fisk NM, Glover V (1998): Fetal exposure to maternal cortisol. Lancet; 352: 707-708.
100. Giudice LC, Conover CA, Bale L, Faessen GH, Hg K, Sun I, Imani B, Suen L-F, Irwin JC, Christiansen M, Overgaard MT & Oxvig C (2002): Identification and regulation of the 1GFBP-4 protease and its physiological inhibitor in human trophoblasts and endometrial stroma: evidence for paracrine regulation of IGF-II bioavilability in the placental bed during human implantation. J Clin Endocrinol Metab, 87: 2359-2366.
101. Giudice LC, Mark SP, Irwin JC (1998): Paracrine actions of insulin-like growth factors and IGF binding protein-1 in non-pregnant human endometrium and at the decidual-trophoblast interface. J Reprod Immunol, 39: 133-148.
102. Gluckman PD, Butler JH (1983): Parturition related change in insulin-like growth factors- I and II in the prenatal lamb. Journal of Endocrinology, 99: 223-232.
103. Gluckman PD, Hanson MA (2004): Maternal constraint of fetal growth and its consequences. Semin Fetal Neonatal Med, 9: 419-425.
104. Gluckman PD, Pinal CS (2002): Maternal-Placental-Fetal interactions in the endocrine regulation of fetal growth: role of somatotrophic axes. Endocrine, 19: 81-89.
105. Godfrey K, Robinson S, Barker DJ, Osmond C, Cox V (1996): Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. Br Med J, 312: 410-414.
106. Gonzales LW, Ertsey R, I Ja I lard PL, Froh D, Goerke J, Gonzales J (1990): Glucocorticoids stimulation of fatty acid synthesis in explants of human fetal lung. Biochim Biophys Acta, 1042: 1-12.
107. Goodwin PJ, Ennis M, 'Pritchard KI (2002): Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol; 20: 42.
108. Granado M, Priego T, Martin AI (2005): Anti-inflammatory effect of the ghrelin agonist growth hormone-releasing peptide-2 (GHRP-2) in arthritic rats. Am J Physiol Endocrinol Metab; 288: E486.
109. Greenwood PL, Bell AW (2003): Consequences of intrauterine growth retardation for postnatal growth, metabolism and pathophysiology. Reproduction; 61: 195-206.
110. Gregory A Brent, Douglas S Ross, Kathryn A Martin (2006): Thyroid hormone action, Up To Date ONLINE.
111. Gualillo O, Caminos J, Blanco M, Garcia-Caballero T, Kojima M, Kangawa K (2001): Ghrelin, a novel placental-derived hormone; Endocrinology; 142:788-794.
112. Gude NM, Roberts CT, Kalionis B & King RG (2004): Growth and function of normal human placenta. Thromb Res, 114: 397-407.
113. Haddow, JE, Palomaki, GE, Allan, WC (1999): Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med; 341: 549.
114. Haggarty P (2002): Placental regulation of fatty acid delivery and its effect on fetal growth-a review. Placenta, 23 (Suppl A): S28-S38.
115. Hahn, D, Blaschitz, A, Korgun, ET (2001): From maternal glucose to fetal glycogen: expression of key regulators in the human placenta. Mol Hum Reprod; 7: 1173.

116. Haluzik, M, Nedvidkova, J, Bartak, V (2003): Effects of hypo- and hyperthyroidism on noradrenergic activity and glycerol concentrations in human subcutaneous abdominal adipose tissue assessed with microdialysis. J Clin Endocrinol Metab; 88: 5605.
117. Hamilton GS, Lysiak JJ, Han VK, Lala PK (1998): Autocrine-paracrine regulation of human trophoblast invasiveness by insulin-like growth factor II and IGF-binding protein-1. Exp Cell Res, 244: 147-156.
118. Han VK, Bassett N, Walton J, Challis JR (1996): The expression of insulin-like growth factor (IGF) and IGF-binding protein (IGFBP) genes in the human placenta and membranes for IGF-IGFBP interactions at the feto-maternal interface. J Clin Endocrinol Metab, 81:2680-2693.
119. Han VK, Ercole AJ, Lund PK (1987): Cellular localization of somatomedin mRNA in the human fetus. Science, 236: 193-197.
120. Han VK, Matsell DG, Delhanty PJ, Hill DJ, Shimasaki S, Nygard K (1996): IGF-binding protein mRNAs in the human fetus : tissue and cellular distribution of developmental expression. Horm Res, 45: 160-166.
121. Handwerger S (1991): The physiology of placental lactogen in human pregnancy. Endocrinol Rev; 12: 329-336.
122. Handwerger S and Freemark M (2000): The roles of placental growth hormone and placental lactogen in the regulation of human fetal growth and development. J Pediatr Endocrinol Metab; 13: 343-356.
123. Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS (2002): Weight loss increases circulating levels of ghrelin in human obesity; Clin Endocrinol (OXf); 56(2): 203-206.
124. Haqq AM, Farooqi IS, O-Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL (2003): Serum ghrelin levels are inversely correlated with body mass index, age and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. J Clin Endocrinol Metab, 88(1): 174-178.
125. Harris RBS, Mitchell TD, and Hebert S (2003): Leptin- Induced Changes in body composition in high fat -fed Mice. Experimental Biology and Medicine; 228: 24-32.
126. Harris RBS, Zhou J, REdmann SM, Smagin GN, Smith SR, Rodgers E (1998): A Leptin dose-response study in obese and lean mice . Endocrinology; 139: 8-19.
127. Heini AF, Lara-Castro C, Krik KA, Considine RV,Caro JF, and Weinsier RL (1998): Association of leptin and hunger satiety ratings in obese women. Int J Obes Related Metab Disord; 22: 1084-7.
128. Heinonen S, Taipale P, Sarrikoski S (2001): Weights of placentae from small- for- gestational age infants revisited. Placenta, 22: 399-404.
129. Hernandez-Valencia M, Zarata A, Ochoa R, Fonseca ME, Amato D, De Jesus Ortiz M (2001): Insulin-like growth factor-I, epidermal growth factor and transforming growth factor 3 expression and their association with intrauterine growth retardation, such as development during human pregnancy. Diabetes Obes Metab, 3: 457-462.
130. Herrera E, Amusquivar E, Lopez-Soldado I, Ortega H (2006): Maternal lipid metabolism and placental lipid transfer. Horm Res: 65 Suppl 3: 59.
131. Herrington J, Carter-Su C (2001): Signaling pathways activated by the growth hormone receptor. Trends Endocrinol Metab; 12: 252.
132. Hill DJ (1990): Relative abundance and molecular size of immuno-reactive insulin-like growth factors I and II in human fetal tissues. Early Human Development, 21: 49-58.
133. Hill DJ, Grace CJ, Strain AJ & Milner RD (1986): Regulation of amino acid uptake and DNA synthesis in isolated human fetal fibroblasts and Myoblasts: effect of human placental lactogen, somatomedin-C, multiplication-stimulating activity and insulin. J Clin Endocrinol Metab, 62: 753-760.
134. Hirasawa C, Takeyama J, SAsano H, Fukushima K, Suzuki T, Muramatu Y, Darnel AD, Zaneko C, Hiwatachi N Toyota T, Nagura H, Krozowski ZS (2000): 11 p-hydroxysteroid dehydrogenase type II and mineralocorticoid receptor in human placenta. J Clin Endocrinol Metab, 85: 1306-1309.
135. Ho Y, Liebhaber SA, Cooke NE (2004): Activation of the human GH gene cluster: roles for targeted chromatin modification. Trends Endocrinol Metab; 15: 40.
136. Hollander PM, Asplin CM, Palmer JP (1982): Glucose modulation of insulin and glucagon secretion in non-diabetic and diabetic man. Diabetes; 31: 489.
137. Hosoda H, Kojinia M, Matsuo H, Kangawa K (2000): Ghrelin and deacyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue; Biochem Biophys Res Commun; 279: 909-913.
138. Hosoda H, Kojinia M, Mizushima T, Shimizu S, and Kangawa K (2003): Structural divergence of human ghrelin identification of multiple ghrelin-derived molecules produced by post-translational processing. J Biol Chem, 278: 64-70.
139. Hosoda H, Kojima M, Kangawa K (2002): Ghrelin and the regulation of food intake and energy balance. Mol Interv; 2: 494.
140. Hubbard SR, Wei L, Ellis L, Hendrickson WA (1994): Crystal structure of the tyrosine kinase domain of the human insulin receptor. Nature; 372: 746.
141. Hult M, Jornvall H, Oppermann UC (1998): Selective inhibition of human type 1 11(3- hydroxysteroid dehydrogenase by synthetic steroids and xenobiotics. FEBS Lett, 441: 25-28.
142. Illsley NP (2000): Glucose transporters in the human placenta. Placenta; 21: 14.
143. Jaffe CA, DeMott-Friberg R, Barkan AL (1996): Endogenous growth hormone (GH)-releasing hormone is required for GH responses to pharmacological stimuli. J Clin Invest; 97: 934
144. Jansson T, Powell TL (2000): Placental nutrient transfer and fetal growth. Nutrition; 16-500.
145. Jansson T, Ylven K, Wennergen M, Powell TL (2002): Glucose transport and system A activity in syncytotrophoblast microvillous and basal plasma membranes in intrauterine growth restriction. Placenta, 23: 392-399.
146. Jensen GM, Moore LG (1997): The effect of high altitude and other risk factors on birth weight: independent or interactive effects? Am J Public Health, 87: 1003-1007.
147. Jones JL, Ercole AJ, Camcho-Hubner C, Clemmons DR (1991): Phosphorylation of insulin-like growth factor-binding protein 1 in cell culture and in vivo: effects on affinity for IGF-I. Proc Natl Acad Sci USA, 88:7481-7485.
148. Joy C, Sable A, Tschop M, Del Parigi A, Daychild P, Tataranni PA (2003): Cross-sectional and prospective relationships of fasting plasma ghrelin concentrations with anthropometric measures in pima Indian children. J, Clin Endocrinol Metab; 88(8): 3756-3761.
149. Juhan-Vagiie I, Alessi MC, Vague P (1996): Thrombogenic and fibrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus. Ann Med; 28: 371.
150. Kaaks R, Toniolo P, Akhmedkhanov A (2000): Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst; 92: 1592.
151. Kahaly GJ, Dillmann WH (2005): Thyroid hormone action in the heart. EndocrRev; 26:704.
152. Kahn BB. Lilly lecture (1995): Glucose transport: pivotal step in insulin action. Diabetes; 45: 1644.
153. Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I (2000): Central effect of ghrelin, an endogenous growth hormone secretagogue on hypothalamic peptide gene expression. Endocrinology, 141:4797-4800.
154. Keim NL, Stern JS, Havel PJ (1998): Relation between circulating leptin concentration and appetite during a prolonged, moderate energy deficit in women. Am J Clin Nutr; 68: 794-801.
155. Keller U, Gerber PP, Stauffacher W (1988): Fatty acid-independent inhibition of hepatic ketone body production by insulin in humans. Am J Physiol; 254: E694.
156. Keller U, Lustenberger M, Stauffacher W (1988): Effect of insulin on ketone body clearance studied by a ketone body «clamp» technique in normal man. Diabetologia; 31: 24.
157. Kido Y, Nakae J, Accili D (2001): Clinical review 125: The insulin receptor and its cellular targets. J Clin Endocrinol Metab; 86: 972.
158. Kinare AS, Natekar AS, Chinchwadkar MC, Yajnik CS, Coyaji KJ, Fall CH, Howe DT (2000): Low midpregnancy placental volume in rural Indian women: a cause for low birth weight? Am J Obstet Gynecol, 182:443-448.
159. Kitamura S, Yokota I, Hosoda H, Kotani Y, Matsuda J, Naito E, Ito M, Kangawa K, Kuroda Y (2003): Ghrelin concentration in cord and neonatal blood: relation to fetal growth and energy balance. J of Clin Endocr and Metab, 88(11): 5473-5477.
160. Klein I, Ojaniaa K (2001): Thyroid hormone and the cardiovascular system. NEnglJMed; 344:501.
161. Kliman HJ (2000): Uteroplacental blood flow. The story of decidualization, menstruation, and tropho-blast invasion. Am J Pathol, 157: 1759-1768.
162. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K (1999): Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature; 402: 656-660.
163. Korbonits M, Goldstone AP, Gueorguiev M, Grossman AB (2004): Ghrelin – a hormone with multiple functions. Front Neuroendocrinol; 25:27
164. Kramer MS, Kakuma R (2003): Energy and protein intake in pregnancy. Cochrane Database Syst. Rev; CD000032.

165. Kulkarni RN, Bruning JC, Winnay JN (1999): Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. Cell; 96: 329.
166. Lall S, Tung L, Ohlsson C, Jansson J, and Dickson SL (2001): Growth hormone (GH)-independent stimulation of adiposity by GH secretagogues. Biochem Biophys Res Commun; 12: 132-138.
167. Lau M M, Stewart CE, Liu Z, Bhatt H, Rotwei P, Stewart CL (1994): Loss of the imprinted IGF2/cation-independent mannose-6-phosphate results in fetal overgrowth and prenatal lethality. Gene and Development, 8: 2953-2963.
168. Lawrence S, Warshaw JB (1998): Increased binding of epidermal growth factor to placental membranes in IUGR fetal rats. Pediat Res; 25:214-18.
169. Lee PD, Conover CA, Powell DR (1993): Regulation and function of insulin-like growth factor-binding protein-1. Proc Soc Exp Biol Med, 204: 4-29.
170. Leguizamon G, Von Stecher F (2003): Third trimester glycemic profiles and fetal growth. Curr Diab Rep, 3: 323-326.
171. Leung KC, Ho KK (2001): Measurement of growth hormone, insulin-like growth factor I and their binding proteins: the clinical aspects. Clin ChimActa 2001; 313: 119.
172. Liang Y, Cushman SM, Whitesell RR, Matschinsky FM. GLUT1 is adequate for glucose uptake in GLUT2-deficient insulin-releasing beta cells. Horm Metab Res; 29: 255.
173. Liggins GC (1994): The role of cortisol in preparating the fetus for the birth. Reprod. Fertil. Dev., 6: 141-150.
174. Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A (1993): Mice carrying null mutations of the genes encoding insulin-like growth factor I (IGF-I) and type 1 IGF receptor. Cell, 75: 59-72.
175. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS (2001): Maternal asthma and pregnancy outcome: A retrospective cohort study. Am J Obstet Gynecol, 184:90-96.
176. Louvi A, Accili D & Efstratiadis A (1997): Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. Developmental Biology, 189: 33-48.
177. Loy GL, Quick Jr AN, Hay Jr ww, Meschia G, Battaglia FC, Fennessey PV (1990): Fetoplacental deamination and decarboxylation of leucine. Am J Physiol, 259: E492-E497.
178. Ludwig T, Eggenschwiler J, Fisher P, Ercole AJ, Davenport ML, Efstratiadis A (1996): Mouse mutants lacking the type 2 IGF receptor are rescued from perinatal lethality in IGF2 & IGF1R null backgrounds. Developmental Biology, 177: 517-535.
179. Luecke RH, Wosilait WD, Young JF (1999): Mathematical modeling of human embryonic and fetal growth rates. Growth Dev Aging; 63: 49-59.
180. Lumley J (1987): Stopping smoking. Br J Obstet Gynaecol, 94: 289-292.
181. Lusting RH (2001): The neuroendocrinology of childhood obesity, Pediatric, Clinics of North America; 48: 909-930.
182. Lyall F, Bulmer JN, Duffie E, Cousins F, Theriault A, Robson SC (2001): Human trophoblast invasion and spiral artery transformation: the role of PECAM-1 in normal pregnancy, preeclampsia, and fetal growth restriction. Am J Pathol, 158: 713-1721.
183. Madiehe AM, Schafflauser AO, Braymer DH, Bray GA, York DA (2000): Differential expression of leptin receptor in high- and low- fat-fed Osborne-Mendel and S5B/P1 rats. Obesity Research; 8: 467-474.
184. Magnusson AL, Waterman IJ, Wennergren M, Jansson T, Powell TL (2004): Triglyceride hydrolase activities and expression of fatty acid binding proteins in the human placenta in pregnancies complicated by intrauterine growth restriction and diabetes. J Clin Endocrinol Metab, 89: 4607-4614.
185. Mahajan SD, Singh S, Shah P, Gupta N, Kochupillai N (2004): Effect of maternal malnutrition and anemia on endocrine regulation of fetal growth. Endocr Res, 30: 189-203.
186. Mailman, ML, Veldhuis, JD, Thorner, MO (1993): Normal control of growth hormone secretion. Horm Res; 40: 37
187. Mandarino LJ, Printz, RL, Cusi, KA (1995): Regulation of hexokinase II and glycogen synthase mRNA, protein, and activity in human muscle. Am J Physiol; 269: E701.
188. Marconi AM, Paolini C, Buscaglia M, Zerbe G, Battaglia FC, Pardi G (1996): The impact of gestational age and fetal growth on the maternal-fetal glucose concentration difference. Obstet Gynecol, 87: 937-942.
189. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z (2000): Ghrelin stimulates gastric acid secretion and motility in rats.Biochem Biophys Res Commun, 276: 905-908.
190. Matschinsky F, Linag Y, Kesavan P (1993): Glucokinase as pancreatic beta-cell glucose sensor and diabetes gene. J Clin Invest; 92: 2092.
191. Matthews SG, Owen D, Kalabie G, Banjanin S, Setiawan EB, Dunn EA, Andrews Mil (2004): Fetal glucocorticoid exposure and hypothalamo-pituitary-adrenal(HPA) function after birth. Endocr Res, 30: 827-836.
192. McCalla CO, Nacharaju VL, Muneyyirci-Delale O, Glasgow S, Feldman JG (1998): Placental 11 f3-hydroxysteroid dehydrogenase in normotensive and preeclamptic pregnancies. Steroids, 63: 511-515.
193. McCulloch DK, Bingley PJ, Colman PG (1993): Comparison of bolus and infusion protocols for determining acute insulin response to intravenous glucose in normal humans. The ICARUS Group. Islet Cell Antibody Register User's Study. Diabetes Care; 16:911.
194. McTernan CL, Draper N, Nicholson H, Shalder SM, Driver P, Kilby MD, Stewart PM (2001): Reduced placental lip hydroxysteroid dehydrogenase type-II mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. J Clin Endocrinol Metab 86: 4979-4983.
195. McVeigh GE, Brennan GM, Johnston GD (1992): Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia; 35:771.
196. Melmed Shlomo, Peter J Synder; Kathryn A Martin (2006): Up To Date online.
197. Mesiano S, Mellon SH & Jaffe RB (1993): Mitogenic action, regulation, and localization of insulin-like growth factors in the human fetal adrenal gland. J Clin Endocrinol Metab, 76: 968-976.
198. Midgley PC, Holownia P, Smith J, Moore M, Russell K, Oates n, Shaw JC, Honour JW (2001): Plasma cortisol, cortisone, and urinary glucocorticoid metabolites in preterm infants. Biol Neonate, 79: 79-86.
199. Misra M, Miller KK, Stewart V (2005): Ghrelin and bone metabolism in adolescent girls with anorexia nervosa and healthy adolescents. J Clin Endocrinol Metab; 90: 5082.
200. Mundinger TO, Cummings DE, Taborsky GJ Jr (2006): Direct stimulation of ghrelin secretion by sympathetic nerves. Endocrinology; 147: 2893.
201. Murphy KG, Bloom SR (2004): Gut hormones in the control of appetite. ExpPhysiol, 89:507-516.
202. Murphy E, Williams GR (2004): The thyroid and the skeleton. Clin Endocrinol (Oxf); 61: 285.
203. Myatt L (2002): Role of placenta in preeclampsia. Endocrine; 19: 103.
204. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K (2001): A role for ghrelin in the central regulation of feeding. 409: 194-198.
205. Neary NM, Small CJ and Bloom S R (2003): Gut and Mind Gut; 52: 918-921.
206. Newnham JP, Patterson L, James I, Reid SE (1990): Effects of maternal cigarette smoking on ultrasonic measurements of fetal growth and on Doppler flow velpcity waveforms. Early Hum Dev, 24 : 23-36.
207. Ng P.C, Lee C H, Lam C WK, Wong E, Chan I H S, Fok T E (2004): Plasma ghrelin and resistin concentrations are suppressed in infants of insulin-dependent diabetic mother. J of Clin Endocrin and Metab, 89:5563-5568.
208. Ng PC, Lee CH, Lam CWK, Chan HIS, Wong E, Fok TF (2005): Ghrelin in preterm and term newborns: relation to anthropometry, leptin and insulin. Clinical Endocrinology; 63: 217-22.
209. Nordt, TK, Sawa, H, Fujii, S, Sobel, BE (1995): Induction of plasminogen activator inhibitor type-1 (PAI-1) by proinsulin and insulin in vivo. Circulation; 91: 764.
210. Oliver MH, Hading JE, and Breier BH (1996): Fetal insulin -like growth factor IGF-I and IGF-II are regulated differently by glucose or insulin in sheep fetus . Reprrod Fertil Dev; 81(1): 167-172.
211. Onal P Cinaz, Y Atalay, C Turkyilmaz, A Bideci, A Ak turk, N Okumus, S Unal, E Koc, E Ergenekon (2004): Umbilical cord ghrelin concentrations in small- and appropriate- for gestational age newborn infants: relationship to anthropometric markers; Journal of Endocrinology; 180:267-271.
212. Onal E E, Cinaz P, Atalay Y, Turkyilmaz C, Bideci A, Akturk A, Okumus N, Unal S, Koc E, Ergenekon E (2004): Umbilical cord ghrelin concentration in small and appropriate-for-gestational age newborn infants: relation to anthropometric markers. J of Endocrin, 180,267-271.

213. Ong K, Kratzsch J, Keiss W, Costello M, Scott C, Dunger D (2000): Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGFBP and the soluble IGF-II/ mannose-6-phosphate receptor in the term human infants. Journal of Clinical Endocrinology and Metabolism, 85, 4266-4269.
214. Orback Z, Darcan S, Coker M, Goksen D (2001): Maternal and fetal serum insulin-like growth factors I (IGFs). Insulin-like growth factor binding proteins-3(IGFBP-3), leptin levels and postnatal growth in infants born small for gestational age. J Pediat Endocrinol Metab;14(8): 1119-1127.
215. Otto C, Platt LD (1991): Fetal growth and development. Obstetric and Gynecology; 18:907.
216. Pak C Ng, Cheuk H L, Christopher WK, Iris H S, Eric W & Tai F (2005): Ghrelin in preterm and term newborns & relation to anthropometry, leptin & insulin. Clin Endocrinology, 63: 217-222.
217. Pannier EM, Irwin JC, Giudice LC (1994): Insulin-like growth factor binding proteins in the human fetus, Am J Obstet Gynecol, 171: 746-752.
218. Pardi G, Marconi AM, Cetin I (2002): Placental-fetal interrelation-ship in IUGR fetuses-a review. Placenta, 23(Suppl A): S136-S141.
219. Pastraknijic A, Derewlany LO, Koren G (1999): Maternal cocaine use and cigarette smoking in pregnancy in relation to amino acid transport and fetal growth. Placenta, 20: 499-512.
220. Pearson ER, Flechtner I, Njolstad PR (2006): Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med; 355: 467.
221. Peleg D, Kennedy CM, Hunter SK (1998): Intrauterine growth restriction: identification and management. Am Fam Physician, 58: 453-460: 466-467.
222. Picciano MF (2003): Pregnancy and lactation: physiological adjustments, nutritional requirements and the role of dietary supplements. J Nutr, 133: 1997S-2002S.
223. Pong, SS, Channg LP, Dean, DC (1996): Identification of a new G-protein-linked receptor for growth hormone secretagogues. Mol Endocrinol; 10: 57.
224. Potter SM, Dennedy MC, and Morrison JJ (2002): Corticosteroids and fetal vasculature: effects of hydrocortisone, dexamethasone and betamethasone on human umbilical artery. BJOG, 109: 1126-1131.
225. Purnell JQ, Weigle DS, Breen P, Cummings DE (2003): Ghrelin levels correlate with insulin level, insulin resistance, and high-density lipoprotein_ cholesterol, but not with gender, menopausal status, or cortisol level in humans. J Clin Endocrinal Metabolism; 88: 5747-52.
226. Regnault TR, de Vrijer B, Battaglia FC (2002): Transport and metabolism of amino acids in placenta. Endocrine: 19-23.
227. Regnault TR, Marconi AM, Smith CH (2005): Placental amino acid transport systems and fetal growth restriction – a workshop report. Placenta; 26 Suppl A S76.
228. Rich-Edwards JW, Buka SL, Brennan RT, Earls F (2003): Diverging association of maternal age with low birth weight for black and white mothers. Int J Epidemiol, 32: 83-90.
229. Rockwel LC, Vargas E, Moore LG (2003): Human physiological adaptation to pregnancy: inter- and intraspecific perspectives. Am J Human Biology, 15:330-341.
230. Rodger A Liddle, F Xavier Pi-Sunyer, and Kathryn A Martin (2007): Ghrelin; Up to Date Online.
231. Rogerson FM, Kayes KM, White PC (1997): Variation in placental type 2 11(3- hydroxysteroid dehydrogenase activity is not related to birth weight or placental weight. Moll Cell Endocrinol, 128: 103-109.
232. Romon M, Lebel P, Velly C, Marecaux N, Fruchart JC and Dallongeville J. (1999): Leptin response to carbohydrate or fat meal and association with subsequent satiety and energy intake. Am J Physiol; 277:E855-61.
233. Rosenfield RL, Barnes RB, Cara JF, Lucky AW (1990): Dysregulation of cytochrome P450c 17 alpha as the cause of polycystic ovarian syndrome. Fertil Steril; 53: 785.
234. Rotmensch S, Liberati M , Vishne TH, Celentano C, Ben-Rafael Z, Bellati U (1999): The effect of betamethasone and dexamethasone on fetal heart rate pattern and biophysical activities. A prospective randomized trial. Act Obstet Gynecol Scand, 78: 493-500.
235. Saltiel AR, Kahn CR (2001): Insulin signalling and the regulation of glucose and lipid metabolism. Nature; 414: 799.
236. Salzman A, Wan CF, Rubin CS (1984): Biogenesis, transit, and functional properties of the insulin proreceptor and modified insulin receptors in 3T3-L1 adipocytes. Use of monensin to probe proreceptor cleavage and generate altered receptor subunits. Biochemistry; 23: 6555.
237. Schaller G, Schmidt A, Pleiner J, Woloszczuk W, Wolzt M, Luger A (2003): Plasma ghrelin concentrations are not regulated by glucose or insulin: a double- blind, Placebo controlled crossover clamp study. Diabetes; 52: 16-20.
238. Schoen RE, Tangen CM, Kuller LH (1999): Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst; 91: 1147.
239. Schoof E, Girstl M, frobenius W, Kirschbaum M, Dorr HG, Rascher W, Dotsch J (2001): Decreased gene expression of 11 (3-hydroxysteroid dehydrogenase type 2 and 15-hydroxyprostaglandin dehydrogenase in human placenta of patients with preeclampsia. J Clin Endocrinol Metab, 86: 1313-1317.
240. Serradeil-Le Gal C, Raufaste D, Brossard G, Pouzet B, Marty E, Maffrand JP (1997): Characterization and localization of leptin receptors in the rat kidney. FEBS Letters; 404: 185-191.
241. Settle P, Mynett K, Speake P (2004): Polarized lactate transporter activity and expression in the syncytiotrophoblast of the term human placenta. Placenta; 25: 496.
242. Shams M, Kilby MD, Somerset DA, Howie AJ, Gipta A, Wood PJ, Afnan M, Stewart PM, (1998): 11 hydroxysteroid dehydrogenase type II in human pregnancy and reduced expression in intrauterine growth restriction. Hum Reprod, 13: 799-804.
243. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M, et al. (2002): Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion; The Journal of Clinical Endocrinology & Metabolism; 87: 240-244.
244. Shore VH, Wang TH, Wang CL (1997): Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. Placenta; 18: 657.
245. Shuto Y, Shibasaki T, Otagiri A, Kuriyama H, Ohata H, Tamura H (2002): Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding and adiposity. J Clin Invest; 109(11): 1429-1436.
246. Sibley C, Glazier J D, Greenwood SL, Lacey H, Mynett K, Speake P, Janson T, Johansson M, Powell TL (2002): Regulation of placental transfer: the Na(+)/H exchanger- a review placenta, 23(Suppl A) S39-S46.
247. Sibley C, Glazier J, D Souza S (1997): Placental transporter activity and expression in relation to fetal growth. Exp Physiol, 82: 389-402.
248. Sinha MK, Ohannesian JP, Heiman ML, Kriauciunas A, Stephens TW, Magosin S (1996): Nocturnal rise of leptin in lean, obese, and non-insulin-dependant diabetes mellitus subjects! Clin Invest; 97: 1344-7.
249. Sorensen S, Von Taboullit D, Schioler V, Griesen G, Petersen S, Larsen T (2000): Serial measurements of serum human placental lactogen (hPL) and serial ultrasound examination in the evaluation of fetal growth. Early Hum Dev, 60: 25-34.
250. Soriano-Guillens L, Barrios V, Chowen J, Sanchez I, Vila S, Quero J (2004): Ghrelin levels from fetal life through early adulthood: Relationship with endocrine, metabolic and anthropometric measures. J Pediatr, 144(1): 36-42.
251. Sperling MA, Menon RK (1999): Hyperinsulinemic hypoglycemia of infancy. Recent insights into ATP-sensitive potassium channels, sulfonylurea receptors, molecular mechanisms, and treatment. Endocrinol Metab Clin North Am; 28: 695.
252. Stenvinkel P, Pcoits-Filho R, Lindholm B (2003): Leptin, Ghrelin and proinflamatory cytokines: Compounds with nutritional impact in chronic kidney disease! Advances in Renal Replacement Therapy; 10:332-345.
253. Stewart PM, Rogerson FM, Mason JI (1995): Type II 11 3-hydroxysteroid dehydrogenase mRNA and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidegenesis. J Clin Endocrinol Metab, 80: 885-890.
254. Stralfors P, Bjorgell P, Belfrage P (1984): Hormonal regulation of hormone-sensitive lipase in intact adipocytes: identification of phosphory-lated sites and effects on the phosphorylation by lipolytic hormones and insulin. Proc Natl Acad Sci USA; 81: 3317.
255. Stumvoll M, Meyer C, Mitrakou A (1997): Renal glucose production and utilization: new aspects in humans. Diabetologia, 40: 749.
256. Sturm K, Macintosh CG, Parker BA, Wishart J, Horowitz M, and Chapman IM (2003): Appetite, food intake and plasma concentration of cholecystokinin, ghrelin and other gastrointestinal hormones in undernourished old women and well nourished young and older women. J Clinical Endocrinology and Metabolism; 88: Number 8.
257. Subtil D, Tiberghien P, Devos P, Therby D, Lecrec G, Vaast P, Puech F (2003): Immediate and delayed effects of antenatal corticosteroids on fetal heart rate; Am J Obstet Gynecol, 188: 524-531.

258. Sulovic V (2002): Placental proteins and proteins hormones in high risk pregnancies . Glas Sip Akad Nauka Med; 47: 1-19.
259. Sun IY, Overgaard MT, Oxvig C, Giudice LC (2002): Pregnancy-associated plasma protein A proteolytic activity is associated with the human placental trophoblast cell membrane.J Clin Endocrinol Metab, 87: 5235-5240.
260. Sun Y, Wang P, Zheng H, Smith RG (2004): Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. Proc Natl Acad Sci USA; 101: 4679.
261. Tschop M, Statnick MA, Suter TM, Heiman ML (2002): GH-releasing peptide-2 increase fat mass in mice lacking NPY: indication for a crucial mediating role of hypothalamic agouti related protein; Endocrinology; 143: 558-568.
262. Takaya K, Ariyasu H, Kanamoto N (2000): Ghrelin strongly stimulates growth hormone release in humans. J Clin Endocrinol Metab; 85: 4908.
263. Tamas L, Diano S, Sotonyi P, Heiman M, Tschop M (2001): Minireview: Ghrelin and the regulation of energy balance; Endocrinology; 142:4163-4169.
264. Tanaka M, Naruo T, Muranaga T, Yasuhara D, Shiiya T,Nakazato M (2002): Increased fasting plasma ghrelin levels in patient with bulimia nervosa; Eur J Endocrinol; 146 R1-R3.
265. Thakur A, Sasen M, Lee JJ, Thakur V, Buchmiller TL (2000): Ontogeny of insulin-like growth factor 1 in a rabbit model of growth retardation. Journal of Surgical Research, 91, 135-140.
266. Thaler I, Manor D, Itskovitz J, Rotten S, Levit N, Timor-Tritsch I, Brandes JM (1990): Changes in uterine blood flow during human pregnancy. Am J Obstetric and Gynecology, 162: 121-125.
267. Thompson NM, Gill DA, Davies R, Loveridge N, Houston PA, Robinson C (2004): Ghrelin and des-octanyl ghrelin promote adipogenesis directly in vivo by a mechanism independent of the type la growth hormone secretagogue receptor; Endocrinology; 145:234-242.
268. Toshinai K, Date Y, Murakami N, Shimado M, Mondal MS, Shimbara T (2003): Ghrelin- induced food intake is mediated via the orexin pathway. Endocrinology; 144: 1506-1512.
269. Tschop M, Smiley DL and Heiman ML (2000): Ghrelin induces adiposity in rodents. Nature; 407: 908-913.
270. Tshop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, and Heiman ML (2001): Circulating ghrelin levels are decreased in human obesity; Diabetes; 50: 707-709.
271. Unger RH (2004): The hyperleptinemia of obesity-regulator of caloric surpluses. Cell; 117: 145.
272. Van Canter, E, Leproult R, Plat L (2000): Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA; 284: 861.
273. Vanessa E. Murphy, Roger Smith, Warwick B. Giles, Vicki L. Clifton (2006): Endocrine reviews, 27(2): 141-169.
274. Vatten LJ, Nilsen ST, Odegard RA, Romundstad PR, Austgulen R (2002): Insulin-like growth factor I and leptin in umbilical cord plasma and infant birth size at term. Pediatrics, 109: 1131-1135.
275. Veldhuis JD, Zhang G, Garmey JC (2002): Troglitazone, an insulin- sensitizing thiazolidinedione, represses combined stimulation by LH and insulin of de novo androgen biosynthesis by thecal cells in vitro. J Clin Endocrinol Metab; 87: 1129.
276. Victoria R, Leslie M, Charles JL, Vanessa AB (2008): Uptodate Online.
277. Wang HS, Perry LA, Kanisius J, lies RK, Holly JM, Chard T (1991): Purification and assay f insulin-like growth factor-binding protein-1: measurement of circulating levels throughout pregnancy. J Endocrinol, 128: 161-168.
278. Wang ZQ, Fung MR, Barlow DP, Wagner EF (1994): Regulation of embryonic growth and lysosomal targeting by the imprinted igf2/Mpr gene. Nature, 372: 464-467.
279. Waters M, Considine RV, van Gaal LF (2000): Human leptin: from an adipocyte hormone to an endocrine mediator. Europian journal of Endocrinology; 143:293-311.
280. Waters MJ, Kaye PL (2002): The role of growth hormone in fetal development. GH and IGF Res, 12: 137-146.
281. Wathes DC, Reynolds TS, Robinson RS, Stevenson KR (1998): Role of the insulin-like growth factor systems in uterine function and placental development in ruminants. Journal of Dairy Science, 81: 1778-1789.
282. Watson SJ, Ln X, Bagnol D, Barsh G, Gantz I, and Akil H, POMC and Agrp (1999): relationships and complexities (Abstract). In Proceedings of the American Neuroendocrine Society, Neuroendocrine Workshop, San Diego, CA 1999, San Diego CA, ANS 1999; p32.
283. Weiss RE, Refetoff S (1996): Effect of thyroid hormone on growth. Lessons from the syndrome of resistance to thyroid hormone. Endocrinol Metab Clin North Am; 25: 719.
284. Westwood M (1999): Role of insulin-like growth factor binding protein 1 in human pregnancy.Rev Reprod, 4: 160-167.
285. Westwood M, Gibson JM, White A (1997): Purification and characterization of the insulin-like growth factor-binding protein-1 phosphoform found in normal plasma. Endocrinology, 138: 1130-1136.
286. Wierup N, Sundler F (2004): Circulating levels of ghrelin in human fetuses. Europian Journal of Endocrinology, 150: 405.
287. Williams SB, Cusco JA, Roddy MA (1996): Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J Am Coll Cardiol; 27: 567.
288. Williams SB, Goldfine AB, Timimi FK (1998): Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. Circulation; 97: 1695.
289. Woods KA, Camacho-Hubner C, Savage M, Clark AJL (1996): Intrauterine growth retardation and postnatal growth failure associate with deletion of die insulin-like growth factor I gene. New England Journal of Medicine, 335: 1363-1367.
290. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG (2001): ghrelin enhances appetite and increases food intake in humans J Clin Endocrinol Metab; 86: 5992-5995.
291. Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S (2000): The novel hypothalaqmic peptide ghrelin stimulate food intake and growth hormone secretion; Endocrinology; 141: 4325-4328.
292. Wu Y, Koenig RJ (2000): Gene regulation by thyroid hormone. Trends Endocrinol Metab; 11: 207.
293. Yeh TF, Lin YG and Hsieh WS (1997): Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicentre clinical trail. Pediatrics; 100: 4.
294. Yokota I, Kitaniura S, Hosoda H, Kotani Y, Kangawa K (2005): Concentration of active form of ghrelin in fetal and neonatal circulation. J of Endocrinol, 52: 271-276.
295. Yoshihara F, Kojima M, Hosoda H, Nakazato M, Kangawa K (2002): Ghrelin: a novel peptide for growth hormone release and feeding regulation; Curr Opin Clin Nutr Metab Care; 5: 391-395.
296. Yoshimoto A, Mori K, Sugawara A, Mukoyama M, Yahata K, Suganami T (2002): Plasma ghrelin and deacyl ghrelin concentration in renal failure; J Am SocNephrol; 13: 2748-2752.
297. Zanardo V, Giacobbo F, Zambon P, Trevisanuto D, Griffifth P, Grella P, Zacchello G (1990): Antenatal aminophyline and steroid exposure effects on glomerular filtiration rate and renal sodium excretion in preterm newborns. J Perinat Med, 18: 283-288.
298. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994): Positional cloning of the mouse obese gene and its human homologue. Nature; 372: 425-432.
299. Zhang JV, Ren PG, Avsian-Kretchmer O (2005): Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science; 310: 996.
300. Zygmunt M, Herr F, Munsted K, Lang U, Liang OD (2003): Angiogenesis and vasculogenesis in pregnancy. Eur J Obstet Gynecol Reprod Biol, 110 (Suppl 1): 510-518.

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Физиология и регулирование развития плода (часть 1)

Среда, в которой развивается плод, играет важную роль в его росте и развитии и имеет решающее значение для выживания плода и формирования его здоровья на длительный срок [215].

Регулирование нормального роста плода включает в себя множество разнонаправленных взаимодействий между матерью, плацентой и плодом. Мать поставляет питательные вещества и кислород к плоду через плаценту. При этом синтезируются гормоны плаценты, которые регулируют обмен веществ у матери. Итак, плацента является местом обмена между матерью и плодом. Она регулирует рост плода через синтез таких гормонов как IGFs и глюкокортикоиды. Адекватное вторжение трофобласта на ранних сроках беременности и повышение маточно-плацентарного кровотока обеспечивают достаточный рост матки, плаценты и плода. Плацента может реагировать на эндокринные сигналы плода для увеличения транспорта материнских питательных веществ. Продукция плацентарных гормонов влияет на физиологию и даже поведение матери.

Влияние матери на рост и развитие плода

Материнский геном и окружающая среда. Нормальное развитие плода связано с увеличением числа и размера, которые становятся доминирующими после 32 недель беременности. Рост и развитие плода зависят как от генетических факторов, так и от факторов окружающей среды. Материнские гены имеют важное влияние на рост плода [221]. В частности, рост матери соотносится с размерами матки и формирует потенциал для роста плода, являясь основным фактором, определяющим размер плода. Несмотря на то, что масса тела при рождении похожа и сопоставима между братьями и сестрами, известно, что воздействие окружающей среды также играет важную роль в процессе роста [103].

При беременности с использованием донорской яйцеклетки установлено, что на массу тела при рождении влияют только гестационный возраст и вес матери, в то время как вес донора-матери не был связан с массой тела ребенка при рождении. Эти исследования показывают, что среда матки является ключевым фактором роста плода [36]. Получены данные об ограниченных возможностях матки для поддержания роста плода. Это может быть связано с недостаточным количеством питательных веществ или повышенной потребностью, например в случае многоплодной беременности [104].

Мать является поставщиком кислорода и необходимых питательных веществ к плоду через плаценту. Питание матери, его калорийность и метаболизм имеют важное значение в обеспечении питательными веществами плода. Кроме того, изменения в материнском обмене веществ в ответ на гормональные сигналы обеспечивают перенаправление необходимых питательных ингредиентов через плаценту и молочную железу [222].

Повышенное потребление калорий жизненно необходимо во II и III триместрах беременности, чтобы справиться с потребностями растущего плода и плаценты [221].

Потребление белка может быть особенно важным, в то время как некоторые исследования показали связь между низким потреблением белка женщиной на поздних сроках беременности и снижением массы тела ребенка при рождении [105]. В то же время другие исследователи не обнаружили влияния протеиновых добавок на рост плода у матерей, которые недоедают [45]. Однако пополнение калорий или специальные витамины для женщин, страдающих от недоедания, может увеличить массу тела ребенка при рождении в условиях острого и хронического дефицита таких питательных веществ [221]: фолиевая кислота, железо и витамин А.

В Кокрановском систематическом обзоре шести рандомизированных контролируемых исследований было показано, что употребление сбалансированных белково-энергетических добавок снизило риск рождения детей с низкой массой для примерно на 30% [164].

Важным питательным веществом для роста плода является глюкоза. Обследования женщин-диабетиков показали, что низкий уровень глюкозы в крови во время беременности в результате чрезмерно жесткого контроля гликемии приводит к большей заболеваемости новорожденных, рождению детей с низкой массой тела, тогда как высокий уровень глюкозы в крови способствует формированию макросомии [170].

Различные источники белка могут влиять на развитие плода в связи с особенностями их аминокислотного и микроэлементного состава. Существует связь между видом белка пищи, массой плаценты и длиной бедра плода [52, 105].

Кровоток маточной артерии. Увеличение маточного кровотока имеет важное значение для удовлетворения метаболических потребностей со стороны растущей матки, а также плаценты и плода [161]. Всего объем крови у матери увеличивается примерно на 40% во время беременности [229], а общий маточно-плацентарный кровоток составляет 25% от сердечного выброса [161].

Талер и соавт. обнаружили, что во время беременности объемный расход маточной артерии возрастает более чем в 3 раза частично под влиянием увеличения диаметра артерии и снижения сопротивления потока крови [266]. Кроме увеличения маточного кровотока при нормальной беременности, развитию новых кровеносных сосудов в матке, возможно, способствовал синтез плацентарных гормонов: человеческий хорионический гонадотропин (ХГЧ) и IGF2 [300]. При использовании доплеровской оценки маточных артерий в 23 недели беременности установлено, что сопротивление кровотоку сопровождалось повышенным риском рождения детей с малой для гестационного возраста массой тела [4].

Гипоксия матери также влияет на рост плода, и этот эффект не зависит от ее социально-экономического статуса, курения, гипертонии, вызванной беременностью и многоплодия [140].

То же касается и наличия у матери воспалительных заболеваний, которые могут способствовать снижению роста плода. Исследовано влияние бронхиальной астмы у матери на развитие плода и плацентарную функцию. Предварительные эпидемиологические исследования связывают наличие бронхиальной астмы у матери с повышенным риском низкой массы тела у ребенка при рождении [174], однако механизмы такого влияния еще изучены плохо.

Материнское курение ассоциируется со снижением массы тела ребенка при рождении в два раза больше, чем у некурящих и имеет дозозависимый эффект [180]. Низкая масса тела при рождении ребенка ассоциируется с увеличением возраста матери [13, 228]. Механизм влияния курения матери связывают как с более высоким уровнем угарного газа в крови матери, который проникает через плаценту к плоду, что приводит к гипоксии тканей плода, так и с вазоконстрикторным влиянием никотина [206].

Кроме того, выявлена взаимосвязь между материнским курением и ее недостаточным питанием, которые негативно влияют на рост плода. Курящие люди по сравнению с некурящими хуже питаются за счет подавления аппетита никотином. Компоненты табачного дыма влияют на транспорт аминокислот от матери к плоду. В эксперименте in vitro была продемонстрирована способность никотина снижать активность основного натрий-зависимого транспортера микроворсинок мембраны, что приводит к задержке внутриутробного развития (ЗВУР) [85].

Также изменения в аминокислотном транспорте имеют важное значение для развития ЗВУР в связи с небольшой разницей между плацентарной емкостью для транспортировки аминокислот и потребностей плода [219].

Развитие плаценты является строго регулируемым процессом, который необходим для нормального развития плода и поддержания здоровой беременности. Таким образом, плацента выполняет несколько важных функций в качестве интерфейса между матерью и плодом: предотвращает отторжение плода, способствует адекватному прикреплению трофобласта, увеличению маточно-плацентарного кровотока во время беременности, транспортировке и метаболизму пита-

тельных веществ, таких как глюкоза и аминокислоты от матери к плоду, а также синтезу и передаче регулирующих рост плода гормонов и пептидов [276].

Плацента принимает и передает эндокринные сигналы и матери, и плода [3, 158]. При задержке роста плода площадь поверхности плацентарных ворсинок и объем плаценты уменьшаются [158]. Адекватный рост плаценты имеет важнейшее значение для адекватного развития плода. У новорожденных с малой для их гестационного возраста массой тела значительно снижена и масса плаценты по сравнению с детьми с должной массой тела при рождении [128].

Функции плаценты

Вторжение трофобласта и увеличение маточно-плацентарного кровотока. Адекватное вторжение трофобласта, необходимое для поддержания роста плода, когда бластоцисты придерживаются матки, эмбриональные клетки трофобласта дифференцируются в ворсинки и экстраворсинчатые клетки [276; 229]. Миграция и вторжение экстраворсинок цитотрофобласта в эпителий матки имеют важное значение для повышения маточно-плацентарного кровотока при увеличении срока беременности [229]. Спиральные маточные артерии превращаются в крупные сосуды с низким сопротивлением, которые способны транспортировать большее количество материнской крови к плаценте [182].

Отсутствие трофобласт – индуцированных изменений в децидуальной или миометриальном сегментах спиральных артерий является признаком осложнения некоторых беременностей, сопровождающихся задержкой роста плода [161]. Слой клеток синтициотрофобласта, который отличается от клеток цитотрофобласта тем, что в нем синтезируются такие гормоны, как эстрогены, прогестерон, хориоидный гормон человека (ХГЧ), плацентарный лактоген и плацентарный гормон роста для поддержания беременности [104].

Повышенный кровоток во время беременности увеличивает доставку питательных веществ от матери к плоду. Было показано, что у женщин с преэклампсией маточно-плацентарный кровоток был уменьшен до 50%. Также отмечается снижение числа и площади терминала ворсинок при задержке внутриутробного развития плода, что свидетельствует о «неисправности» васкуляризации при таких беременностях [300].

Многие исследования доказывают важность прикрепления трофобласта, изменения в маточно-плацентарном кровотоке и потоке пуповинной крови для поддержания соответствующего роста плода, благодаря доставке ему кислорода и питательных веществ [13, 84, 18, 68].

Плацента является метаболически активным органом, который извлекает 40–60% от общего уровня глюкозы и кислорода, поставляемых в матку [22]. Остальные питательные вещества и метаболиты передаются через плаценту к плоду путем пассивной диффузии, облегченной диффузии, активного транспорта, эндо- и экзоцитоза [247].

Транспорт питательных веществ путем пассивной диффузии (кислород, углекислый газ и карбамид) ограничен плацентарной областью обмена и кровообращения. Облегченная диффузия (глюкоза и лактат) включает в себя передачу вниз по градиенту концентрации носителей молекул, без затрат дополнительной энергии. Активный транспорт требует наличия как белков-носителей, так и использования дополнительной энергии [22]. Плацентарная передача питательных веществ растет параллельно с ростом плода за счет увеличения скорости кровотока [247].

Респираторный газообмен. Кислород и углекислый газ являются липофильными молекулами, которые будут проникать через плаценту по механизму простой диффузии. Плацентарные мембраны имеют высокую проницаемость для O_2 и CO_2, таким образом кровоток ограничивает скорость обмена дыхательных газов через эту ткань. Парциальное давление и разница в сродстве к O_2 между материнским и фетальный гемоглобином – это два важных фактора, которые определяют их усвоение [43].

Для роста плода также необходимы аминокислоты, поскольку они являются компонентами для синтеза белка. Кроме того, их деградация и взаимопревращение промежуточных субстратов приводят к синтезу

или глюкозы или кетоновых тел. Плацента играет важную роль в доставке аминокислот для плода. Этот процесс состоит из трех основных этапов: поступление от матери через мембраны микроворсинок, транспорта через трофобласт цитоплазмы и транспорта через базальную мембрану в пупочное кровообращение [227]. Транспортные системы в трофобласте могут быть как натрий-зависимыми, так и натрий-независимыми и различаются в зависимости от их ионных субстратов [227; 144]. Аминокислоты могут быть усвоены через плаценту. Например, лейцин дезаминируется в плаценте и передается плоду [177].

При задержке роста плода появляются изменения в аминокислотном транспорте аминокислоты через плаценту и поглощении ее плодом. Плод может влиять на экспрессию плацентарных транспортеров аминокислоты в ответ на замедление своего роста.

Исследования, проведенные на трансгенных мышах, лишенных IGF – II гена показало, что у них было уменьшение пассивной диффузии питательных веществ на фоне уменьшения роста. Также отсутствовало регулирование активного транспорта аминокислот, как компенсаторного механизма в плане улучшения роста плода.

Транспорт глюкозы. Глюкоза является основным источником энергии для человеческого плода и плаценты, поскольку она основной субстрат для окислительного метаболизма плода. При этом эффективная передача глюкозы через плаценту имеет важное значение для нормального развития плода. Плацента сама по себе не способна производить значительное количество глюкозы в течение всего периода беременности [276]. Плод также производит минимальное количество сахара, что требует транспорта глюкозы от матери для синтеза гликогена. Процесс транспорта глюкозы от матери осуществляется за счет облегченной диффузии с использованием транспортеров как матери, так и трофобласта плода [188].

Достаточное количество транспортера-1 глюкозы содержится в микроворсинках оболочки синцитиотрофобласта, что в три раза выше, чем в базальной мембране [142, 21].

При нормальном течении беременности формируется состояние резистентности к инсулину, чтобы увеличить доступность глюкозы для плода. Резистентность к инсулину усиливается при беременности у женщин с сахарным диабетом на фоне гипергликемии. Указанное приводит к гипергликемии плода с повышением продукции инсулина, инсулиноподобного фактора роста-1 (ИФР-1) и лептина, что приводит к фетоплацентарной недостаточности [203].

Гипогликемия у детей с малой для их гестационного возраста массой тела может быть связана с уменьшением потребности в переносе глюкозы через плаценту [72]. При исследовании перфузии базовый уровень потребления глюкозы был выше у недоношенных со ЗВУР. В то же время не было никаких изменений в передаче глюкозы к плоду со стороны плаценты [46, 142].

Другое исследование показало, что у матери и плода градиент концентрации глюкозы был увеличен в зависимости от клинической тяжести ЗВУР. Указанное, возможно, имеет адаптивную роль для поддержания транспорта глюкозы через плаценту [188].

Транспорт жирных кислот. Жирные кислоты необходимы для развития плода как источник энергии, а также в качестве прекурсора для ряда важных биологически активных соединений, таких как простагландины и тромбоксан. В III триместре беременности жирные кислоты необходимы для изменений в составе тканей плода, особенно мозга и жировой ткани [276].

Плацента имеет значительный потенциал для усвоения жира и транспорта жирных кислот. Поглощение жира включает в себя распад триглицеридов (из материнской жировой ткани) на свободные жирные кислоты и глицерин, а также реэстерификацию из внутриклеточного фосфат глицерина [276].

Свободные жирные кислоты, а также белки передаются через микроворсинки и базальную мембрану [114]. Уровни незаменимых жирных кислот и линолевой кислоты в плаценте оказались значительно выше у плодов с задержкой внутриутробного развития плода по сравнению с плодами, у которых

масса тела соответствовала гестационному возрасту [218], что может иметь значение для внутриутробного развития мозга [60].

Недавно было обнаружено, что у недоношенных детей активность липазы, гидролазы, липопротеинов и триглицеридов в микроворсинах мембраны уменьшены, что ограничивает внутриутробное развитие плода [184].

Метаболические и эндокринные функции. Метаболические и эндокринные функции плаценты очень сложны, касаются производства гормонов и обмена веществ и должны жестко контролироваться для того, чтобы обеспечить нормальное развитие плода, развитие и поддержание здоровой беременности [276].

Метаболические функции: плацента способна синтезировать гликоген и холестерин, которые являются источником энергии для развивающегося плода. Кроме того, холестерин является важным условием для производства гормонов в фетоплацентарной единице.

Синтез гликогена. Плацента способна синтезировать значительное количество гликогена, который сохраняется в качестве энергетического резерва. Поглощение глюкозы из материнского кровообращения ограничено по скорости рядом ферментов и регуляторов. Особое значение имеет фермент гликогена, который имеет выраженное высокое сродство к GLUT-3 транспортеру в эндотелии, базальной децидуальной оболочке и способствует его внедрению в дополнительные ворсинки трофобласта в плаценте человека [115].

Синтез холестерина. Потребность в холестерине у плода высока, и в ранние сроки беременности количество материнского холестерина в значительной степени соответствует этой потребности. В конце беременности плод сам синтезирует холестерин, используя запас жирных кислот плаценты, созданный из накопленного матерью жира в ранние сроки беременности. Холестерин плаценты является важным условием для выработки плацентой прогестерона и эстрогенов [130].

Обмен белков. Обмен белков в плаценте в значительной степени определяется требованиями роста плода во время беременности. На 10-й неделе беременности производство белка плацентой составляет примерно 1,5 г в день, но с увеличением срока этот показатель возрастает до 7,5 г в день [23].

Лактат в обмене веществ. Лактат является отходом в обмене веществ и выделяется в больших количествах через плаценту, а следовательно, должен быть эффективно удален. L – лактат-транспортеры действуют на микроворсины оболочка плаценты человека и присутствуют на базальной мембране [241].

Эндокринные функции. При беременности плацента является важным органом эндокринной системы. Плацента не иннервируется, поэтому для связи между матерью и плодом должна включаться гуморальная регуляция. Сигнальные молекулы, выделяемые плацентой, могут действовать локально путем паракринного и аутокринного регулирования. Плацента, будучи органом эндокринной системы, отвечает за выработку гормонов у матери и плода. Основным местом производства плацентарных гормонов есть трофобласт и ворсинки хориона [276].

Вопросы, касающиеся гормональной регуляции роста плода и новорожденного ребенка, будут представлены во второй части статьи.