Metabolism of the Fetus during Pregnancy

Introduction:

Fetal metabolism is an extremely important function of the fetus and is assumed to help in maintaining its growth and development and a great deal of it is now known to many researchers. In spite of possessing insight and knowhow’s of fetal metabolism, there is still no direct co-relation about the influence of the fetal metabolism and its effect in the control on the fetal growth, development and maturation process. The three most important factors that are assumed to control the fetal growth and development are the maternal supply of nutrients and hormones to the fetus via the mother’s own metabolic activities along with the transplacental exchange and blood supply. The third important criterion is the indigenous fetal metabolism itself. (1)

Carbohydrate metabolism by the fetus:

During the fetal life, the fetus is constantly supported by maternal glucose from the maternal circulation. Research group from Kolkata for the first time revealed the cause of high fetal sugar as found in some cases. All published research and literature suggests that the fetal blood contains sugar at a lesser concentration than the natural level. (2, 3)

The research group under Dr. Chameli Ganguly further concluded that of the normal glucose level of mothers, 16% showed high blood sugar level in the fetuses in potentially diabetic mothers and about a half showed high blood glucose levels in the fetuses than the mother. In diabetic mothers, a third showed higher blood glucose concentration in the fetuses. It was further observed that the glycogen content of the skeletal muscles is low at 9-12 weeks of (0.4%). (4) However, from 13 to 24 weeks, there is an increase in the muscle glycoprotein content (approximately 1%) which remained more or less steady. Also glycogen content when compared between liver and skeletal muscles in 9-12 weeks of fetuses showed a higher level in the skeletal muscles with respect to the liver. Thereafter with increase in gestation time, the liver and skeletal muscle glycogen content became more or less the same. (4) Also with further age of the fetus, liver became the principal centre for glycogen storage when compared to the skeletal muscles. During 13-16 weeks and 17-20 weeks the activity of the fetal liver becomes one fifth of the adult liver. Further studies on fetal liver revealed that from 9 to 21 weeks, the total inorganic phosphate contents in the liver are higher. (4) Further work by the same research group elucidated the fact that in the 9-12 weeks of fetal development, no glucose-6-phosphatase was detected. The earliest evidence for its activity was found at 14.5 weeks of gestation which increased thereafter. However, even at 24 weeks of gestation, the enzyme activity was still lower than the adult liver. (4) Capkona and Jirasek through their studies found that about 0.34 % of glycogen at 9 weeks of gestation whereas the research findings of the group in Kolkata suggests the glucose activity at a much lower level of 01. % (5) The reason is still unclear but has to do something with the lower socio-economic background of the mothers; however there was much not difference again in their nutritional status when compared to other studies. (4)

Capkova and Jirasek also stressed on the two spurts of glycogen content during the 14-17 weeks, however the research group from Kolkata found an increase in the content throughout the period up to 22 weeks of gestation. These results were in agreement with those of Villee. (23) Further the group observed that there was no relationship between fetal liver glycogen content and relative glycemic content of the fetus and the human placenta was found to possess Glucose-6-Phosphatase activity at a higher level in the gestation period than later. Measurable activity of the fructose-1, 6-bisphosphate was found to be 11 weeks of gestation onwards and the phosphorylase activity of human fetal liver was found to be very low throughout the gestational period.
**Water content of the fetus:**
In fetuses around 6 months, the total body water content is about 30-40%. (6) About 10 weeks of age, 85% of water is observed where extracellular water content is higher than the intracellular content. However, the content of extracellular water decreases with increase in gestation period. Further the same research group from Kolkata showed that the water content in human fetal livers at different gestation period where it varied from 80.5% of the organs at 8-12 weeks in one group to 77.6% at 25-28 weeks in another group compared to only 69% of water in the liver. (6) The content of Aminopolysaccharides or AMPS at 12-16 weeks old fetuses are higher than that of 29-32 weeks old fetuses. However, the content of uronic acid in the lung was about 4-6 times higher than that of the liver. (6)
Lung contains more water than any other organ except the brain. The water content in liver is 80.5% at 9-12 weeks compared to that of 91% in the lung. AMPS content in the brain do not change much with the increase in the fetal age unlike the lungs where it progressively declines with increase in gestational age. Potassium content in fetal brain is lower than the adult brain also. Also in 17-20 weeks fetuses, large amount of intracellular sodium were present. The enzyme activity of glucosamine-6-phosphate synthetase was six times higher than the brain and lungs compared to that of the liver starting from 8-24 weeks of gestation. The human fetal organs have higher osmotic tension in their body fluids than the adult humans which helps the fetus to remain at a buoyant density in the amniotic fluid.

**Urea Biosynthesis and activity in the fetus:**
Balwin was the first person to assess the evolutionary adaptation of nitrogen excretion in an elegant form. (7, 8) Needham suggested that during the embryo development, the embryo excretes ammonia first and then develops a mechanism for nitrogen excretion which was further supported by the works of Putin in 1957. (9, 10, 11) Miller and Chen showed the low activities of enzymes involved in the urea cycle in the fetal liver of rats; however which increased rapidly after birth. (12) Krebs and Henseleit observed that at 3-4 gestational months, fetal livers can produce urea. Activities of enzymes like Argininosuccinic acid synthetase increases with increase in gestational age from 13.09% in 12-15 weeks of gestation to about 81.97% in the 27-30 weeks time.

The activities of argininosuccinase during the development were shown to steadily increase from 12 to 15 weeks of gestation by the Calcutta researchers. The specific activity was also found to increase along with the increase of argininosuccinase enzyme. By the 30th week of gestation, the enzyme activity was found to be similar to that of the adults. (13) The activity of Arginase was found to be more or less the same throughout the gestation period of 9-30 weeks mainly except in the case of very small fetuses with low weights. Normally five enzymes are required for the production of urea from ammonia and Ornithine transcarbamylase one of the five main enzymes showed 1/32rd rate of the adult activity at 15 weeks of gestation thereby showing the fact that the urea rate is 1/32rd of the adult rate. Argininosuccinase enzyme rate is 1/30th of the adult rate. (13)

The rate of ornithine transcarbamylase enzyme at 15 weeks is 1/32rd part of the rate in adult. Also free ornithine content of fetal liver is found to be higher than reported values of adult liver. Polyamines like putrescine increased with gestational age from 0.34 micromole in 15-18 weeks of gestation fetuses to 3.08 micromole in 21-24 weeks old fetuses. However, a subsequent decrease was also observed with increase in the gestational spermine content from 9 mill micromoles per gram to 113.7 mill micromoles per gram in 15-30 weeks of gestational fetuses. Further the research group led by Prof. K.L. Mukherjee also observed that the urea concentration of the bladder fluids of fetuses were low compared to adult urines therefore the question arises whether they can be called proper urine or not. (13)
Lipid Metabolism in the fetus:
Lipids including cholesterol or CHO and fatty acids or FA’s form an important constituent of the human body thereby representing a very essential requirement for the fetal development. The fetal sources for CHO and FA’s are the endogenous and exogenous metabolic supply. After implantation of the embryo in the uterine walls, CHO determines the embryogenesis and morphogenetic fate of the CNS. (14) For neuronal and visual development, fatty acids and triglycerides play an important role. (15) Therefore lack of CHO can hamper the fetal growth which includes steroid hormones like estrogen extremely important for promoting placental progesterone synthesis. (16, 17) CHO, TG’s and FA’s concentration increases in the maternal plasma and thereby allowing the fetus to rapidly receive and store the fat which exceeds by far of any other available nutrition to the fetus at that point of development. (18) Maternal CHO may increase by the 12th week of gestation whereas Triglycerides or TG’s reach a level of 150-300 % of increase in the 3rd trimester. LDL and HDL are the two important Lipoprotein involved in supporting the placental CHO. (19)

The maternal LP’s increase in VLDL, LDL and HDL allows the uptake of these lipids to the placenta. (20) Also placenta is practically impermeable to TG’s except for fatty acids. Most of the CHO is de novo or synthesized by the fetus itself, thereby making the fetus independent in cholesterol supply. (21) Brain and liver tissues have high demand and requirement of CHO. (22) Since, 19th week of gestation, certain CHO synthesis starts to occur. (23) Up to 20% of the sterol used by the fetus in the 1st trimester originates from maternal CHO and even greater percentage of CHO concentrations can be derived from the placenta. (24) It reaches a peak in the 2nd trimester and around 22-40% in the third trimester. (25) LDL concentration has been shown to be higher in the umbilical artery. (26) Most important marker for CHO from the amniotic fluid is APOE phenotype. (27)However, the concept of the fetus acquiring the maternal CHO still needs to be verified for further confirmations. Most human studies suggest that the maternal CHO contributes to the fetal CHO at early gestational development stages. (28) This CHO uptake by the syncytiotrophoblast layer is both receptor-dependent and independent process. (29)

Receptor-mediated mechanisms involving the passage of CHO are via LDL & VLDL receptors by undergoing endocytosis of the lipoprotein-bound LDL or VLDLR’s. After binding, the ester bonds are degraded and free CHO is transported across the cell via sterol carrier proteins such as sterol carrier protein X, 2 and NPC1L1 or Niemann-Pick-C1-like 1. (30) Further scavenger reporters like SR-B1 with a high affinity towards HDL rather than LDL, LRP-1 or LDL receptor-related protein 1 can cross the plasma membrane without internalization of the receptors. Increase in maternal blood CHO has shown to decrease the LDL receptor proteins in trophoblasts. (31) LRP-2 or megalin binds by HDL through ATP-binding cassettes or ABC transporters like ABCG1 and by aqueous diffusion of ApoE & phospholipid complex. (19) Free fatty acids or FFA’s can be also directly up taken from the maternal circulation and enter the trophoblast cells via passive diffusion or membrane-bound carrier proteins of the fetus. (32, 33) When lipoproteins find it difficult to cross the placenta, triglycerides of T.G.’s become available to the fetus. (20) Two lipases namely the endothelial lipase and lipoprotein lipase or LPL are achieved from FFA’s and LPL is the abundant one in the human placenta having triglyceride lipase activity. Alpha-linolenic acid or ALA and long-chain polyunsaturated fatty acids (LC-PUFA) are transferred to the fetus via the placenta as these cannot be synthesized by the fetus independently. Adequate amount of LC-PUFA is required for proper and normal growth of the fetus. Human fetal adrenal glands make use of LP’s containing CHO and LDL. Early CHO decrease in plasma fetal levels is related to the adrenal gland size. (34) LDL and VLDL are poorly presented in the fetal blood. (35) HLD represents the main lipoprotein in cord blood. (36, 37) ApoA-4, ApoE is up-regulated in the fetal
Glucose Metabolism in the Fetus:
Glucose is the principal blood sugar of the human fetus and it produces half the energy source and its regulation into fetal tissues is regulated by glucose or GLUT transporters. Fetal blood glucose level is comprised of approximately 70-80% of the glucose concentration in the mother's venous blood. The fetus apart from taking glucose from the mother, also utilizes high amount of amino acids thereby depriving the mother and for this reason many mothers develop hypoglycaemia. Fetal metabolism is all about anabolic process due to which glycogen gets stored in the liver and can be accessed during the first hours of birth. Enzymatic activities responsible for gluconeogenesis and glycogenolysis are present in an inactive state in the fetal liver and are activated only in extreme cases of maternal starvation. (41)

Fetal liver contains 3 times more glucose than the liver of an adult which is utilized by the newborn. Also Insulin doesn't pass through the placenta and therefore the fetus has to survive independently in the uterus. Human pancreatic insulin and glucagon concentrations increase with increase in gestational age and are higher in concentration than the adult pancreas. During week 7 to 20 pancreatic hormone secretion increases and small amount of maternal insulin and glucagon becomes detectable at the fetal plasma by week 15. (41)

Role of the Placenta in Metabolism of Drugs and Other Xenobiotics:
The placenta plays an extremely important role as a barrier for the entry of drugs in the fetus especially in the first and early second trimester as the process of organogenesis is initiated in the very early stages of first trimester. Secondly as the organs are still in a developing state, normal adult function of the kidney and liver to metabolize and excrete drug is not expected at this level of development. (42) With the reduction in the fetomaternal barrier in the subsequent trimesters there is also a direct effect on the transportability of the drugs and the role of placenta as a drug metabolizing organ. (43) In the first 10 weeks of fetal development, due to intensive organogenesis, there is a lack of fetomaternal circulation, however this does not entirely removes the chances of embryotoxicity as it has been shown that there are remote still chances of xenobiotic transfer into the fetal compartment by ways of bodily fluid tissue via the intracellular spaces. (42) Entry of lipophilic molecules is usually favoured by the placenta via endocytosis, exocytosis, pinocytosis and the free movement of vesicular vehicles. Passage of lipid insoluble molecules in the absence of transporters is extremely difficult except in cases of extracellular pores. This is also termed as Membrane Limited phenomenon. (44, 45, 46) Stereospecificity is another important parameter for placental exchange only in the case of amino acids. Due to this stereospecificity activity, it was found in animal models that NSAID drugs like (S +)Ketotifen can readily cross the placenta compared to R (-) Ketotifen. (47) Presence of high levels of P-Glycoprotein or PGP, members of the ABC group is also expressed in the syncytiotrophoblast layer therefore forming the essential part of the placental barrier. (48, 49, 50, 51) In the first trimester the expression of Pgp is 45 fold higher compared to the second and third trimester and it subsequently decreases with the increase in gestational time. (52) However expression of other transporters such as the Organic anion transporter or OATP2B1 and the Breast cancer resistance protein BCRP are more or less consistent throughout the first and second trimesters without any noticeable changes. (53) Towards the end of the second trimester, there is an increase in the presence of efflux transporters such as MRP2 or Multi-Drug resistance associated protein 2 or MRP 2. (54, 55) MRP3 whose transportation is still not well understood has shown by researchers to increase with gestational time with the first trimester showing the lowest expression compared to second trimester. Other efflux transporters like MDR1

Plasma also. FA transport proteins expressed by the placenta are FATP 1-4, FATP6, FAT/CD36, and FABP. (38, 39) These further help in secretion of the maternal derived FFA’s into the fetal blood. (40)
and 2 have shown to increase their expression with increase in a gestational stage. MRP5 has shown to be highly expressed in the first trimester as it protects the fetus undergoing organogenesis in the early first trimester. MRP7’s cellular organization is yet to confirmed and is found to be transiently expressed. The main role played by MRP7 is resisting the entry of antiviral drugs and removing nucleotides, bile acids, eicosanoids and conjugated steroids out of the fetal compartment. (42) Therefore, I brief it can be concluded that the drug efflux transporters present on both the mother and the fetal parts of the placenta help in inferring an immunity to the fetus in the absence of complete or partial drug metabolism capabilities of the growing and immature fetus in the first two trimesters.

References:


44. Faber JJ, Thornburg KL. The forces that drive inert solutes from water across the epitheliochorial placenta of the sheep and the goat and the hemochorial placentae of the rabbit and the guinea pig. 1981.


See Also:
Fetus
Metabolism

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