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THE EFFECTS OF INTRAUTERINE GROWTH RETARDATION (IUGR) ON FETAL LUNG CHOLINE KINASE ACTIVITY. Barbara L. Chrzanoska, Rodney E. Ulane, Laura L. Stephenson, Menachem Nitzan, Joseph D. Schulman, NICHD, Bethesda, MD 20014.

The effect of decreased uterine blood supply on one aspect of pulmonary phospholipid metabolism, the developmental pattern of choline kinase (CK), was studied in rats from 17 through 21 days gestation. Sprague-Dawley rats were operated on at the 17th day of pregnancy by ligation of the uterine artery of one horn as described by Wigglesworth (J. Path. Bact. 88:1, 1964) with the opposite horn left untouched (control). On days 18, 19, 20 and 21, fetuses were delivered by C-section and immediately decapitated. The frequency of IUGR fetuses (weighing less than 80% of mean control horn fetuses) in the ligated horn was approximately 50%. The lung wet weight to body weight ratios in the IUGR fetuses were consistently lower than the control litter mates at days 18, 19 and 20. The specific activities of CK were approximately 20% higher in the IUGR fetal lungs on days 20 and 21. No significant differences in CK specific activities were found between sham operated and non-operated controls and lungs from fetuses in the control horns. We conclude that decreased blood supply to the pregnant rat uterus results in a slightly increased activity per mg protein in the lung of the first enzyme of phosphatidylcholine biosynthesis. This increase was not observed in livers from the same fetuses. IUGR fetuses have been reported to show increased amounts of pulmonary phosphatidylcholine and accelerated pulmonary development. Our findings suggest that alterations in CK activity may be involved in this phenomenon.

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FETAL SHEEP PLASMA INSULIN CONCENTRATION AND UMBILICAL LACTATE UPTAKE. Sharon S. Crandell, Frank H. Morriss, Eugene W. Adcock, Robert N. Marshall, and Cherylann Tuchman. (Spon. by R. R. Howell). Univ. of Texas Medical School at Houston, Dept. of Pediatrics, Houston.

To determine the relationship between fetal and maternal plasma insulin concentrations ( $I_f$ ,  $I_m$ ) and umbilical uptake of glucose ( $Q_g$ ) and lactate ( $Q_l$ ) in sheep, 6 ewes of 120-130 days gestation were prepared with indwelling catheters in the umbilical vein, fetal pedal artery and vein, and maternal uterine and femoral arteries. Fed state  $Q_g$ ,  $Q_l$ ,  $I_f$ , and  $I_m$  were determined at intervals from the 2nd to the 11th postoperative day (POD).  $Q_g$  and  $Q_l$  were determined by the Fick principle employing steady state diffusion of antipyrine to determine umbilical blood flow. Studies were performed before (control n=15) and after (n=15) the perfusion of the uterine artery with ovine insulin 7.5 mU/kg ewe/30 min. Insulin was measured by radioimmunoassay.

Results: Control  $I_f$  and  $I_m$  in  $\mu$ U/ml increased with increasing POD as described by the following regression equations:  $I_f = 0.76 \text{ POD} + 3.74$ , (F ratio,  $p < .025$ ), and  $I_m = 1.86 \text{ POD} + 8.61$ , ( $p < .05$ ). Uterine artery insulin infusion increased  $I_m$  but did not affect  $I_f$  or  $Q_l$ . The postoperative increase in  $I_f$  from 5.5-16.0  $\mu$ U/ml was associated with a decrease in  $Q_l$  in mM/min/kg fetus:  $Q_l = -0.004 I_f + 0.072$  ( $p < .025$ ).  $Q_g$  was unrelated to POD,  $Q_l$ , or  $I_f$ .

Conclusions: These studies (1) confirm the lack of ovine insulin transfer across the ovine placenta in vivo, (2) demonstrate increasing  $I_m$  and  $I_f$  for as long as 11 days after surgery and resumption of maternal nutrition, and (3) show that umbilical lactate uptake is inversely related to fetal plasma insulin concentration, but is independent of umbilical glucose uptake and of maternal plasma insulin concentration.

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PARADOXICAL EFFECT OF PROTEIN-BINDING ON PLACENTAL TRANSFER OF STEROIDS. Joseph Dancis, Valerie Jansen, Mortimer Levitz. NYU School of Med. Dept. Ped. and Obstet. & Gynecol., New York City.

The relation of protein-binding to the transfer rates of a series of polar and non-polar steroids has been studied in an *in vitro* perfusion system of human placenta. The clearance indices (C.I. = clearance substrate:clearance antipyrine) for the polar steroids (dexamethasone, betamethasone, prednisolone, cortisol, estriol) from buffer solutions ranged from 0.36 to 0.74. The addition of serum albumin, 1g/dl, to maternal and fetal perfusates had relatively little effect (C.I. 0.25 - 0.51). The C.I. of the non-polar steroids (ethynilestradiol, progesterone, estrone, diethylstilbesterol) from buffer solutions ranged from 0.11 to 0.26. The addition of 1g/dl of serum albumin to the perfusates caused a sharp increase in C.I. (0.52 - 0.83).

Percent binding to serum albumin measured by equilibrium dialysis for the polar steroids were 35 to 60; for the non-polar steroids, 89 to 94. Binding to 20% placental homogenate were 12 to 31 and 60 to 96, respectively.

The transfer of lipid-soluble materials between maternal and fetal plasma is best understood as a series of equilibria in which binding to placenta plays a pivotal role.

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VARIATIONS OF BLOOD OXYGEN AFFINITY AND CONTENT ON CARDIAC OUTPUT (C.O.) AND OXYGEN TRANSPORT TO THE TISSUES IN NEWBORN LAMBS. Maria Delivoria-Papadopoulos, Endla K. Anday, Evan Lipton, James D. Ferguson, Univ. of Pennsylvania, Philadelphia, Pa.

Four groups of two week old lambs were exchange transfused (E.T.) after chronic catheterization. Five lambs, Group I, served as controls; 4 lambs, Group II, received fresh, settled maternal blood; 4 lambs, Group III, received fresh, packed maternal blood and 6 lambs, Group IV, received fresh, packed fetal blood. Cardiac output (C.O.), arterial and venous  $P_{O_2}$ , hematocrit (Hct) and  $P_{50}$  were measured before and two hours after E.T. No significant changes were noted in Group I for all parameters. Mean values for C.O. decreased in all groups following the E.T. (Gr. II by 57% ( $p < 0.01$ ); Gr. III by 14% ( $p < 0.05$ ); Gr. IV by 34% ( $p < 0.025$ ). There were no changes in mean  $P_{aO_2}$  in any of the groups; however, mean  $P_{vO_2}$  increased in Gr. II by 13% ( $p < 0.05$ ), and decreased in Gr. IV by 7% ( $p < 0.025$ ). Mean Hct increased in Gr. II, III and IV by 10%, 48% and 36% ( $p < 0.0025$ ) and mean  $P_{50}$  increased in Gr. II and III by 59 and 43%. These data indicate that with no change in  $P_{50}$  but increased Hct the resulting decreased  $P_{vO_2}$  is in response to a decreased C.O., theoretically compromising  $O_2$  transport to the tissues. With an increased Hct, the decreased C.O. results in no change in  $P_{vO_2}$  presumably counteracted by the increased  $P_{50}$ . In contrast, increased  $P_{50}$  and moderate increased Hct (10%) results in increased  $P_{vO_2}$ , presumably facilitating  $O_2$  transport to the tissues, while maintaining a decreased C.O., thus reducing circulatory demands.

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FETAL LAMB ARGININE VASOPRESSIN (AVP) RESPONSE TO A SINGLE HEMORRHAGE. W.H. Drummond, A.M. Rudolph, L.C. Keil, M.A. Heymann. Department of Pediatrics, University of California, San Francisco and NASA-Ames Research Center, Moffett Field, California.

Hemorrhage (H) has been reported to stimulate AVP release in the fetal lamb. To examine the determinants and time course of the fetal response to H, 7 chronically catheterized fetuses of 92-116 days gestation were hemorrhaged 15-20% of blood volume at a rate of 2%/min. Heart rate, arterial  $P_{O_2}$ ,  $P_{CO_2}$  and pH did not change. Serum AVP, osmolality and hematocrit were drawn at 10 min intervals for 60 min. Blood volume sampled was replaced immediately with fetal blood. AVP was measured by radioimmunoassay. Assay cross reactivity with arginine vasotocin and angiotensin II was negligible. During H, mean systemic arterial pressure (SAP) fell 24% from  $40 \pm 1$  to  $30 \pm 2$  torr ( $p < .01$ ). Serum osmolality did not change H, but rose from  $293 \pm 1.2$  to  $298 \pm 1.9$  mOs ( $p < .05$ ) by 30 min. Serum AVP levels showed a biphasic response. The base line AVP value of  $1.6 \pm .20$  pg/ml rose to  $27.9 \pm 14.9$  ( $p < .01$ ) by the end of H (10 min), then declined to  $16.6 \pm 4.8$  pg/ml at 20 min before rising again to  $34.2 \pm 12.8$  pg/ml by 30 min. Immediately after H, serum AVP correlated inversely with SAP change ( $r = .58$ ), and not with serum osmolality ( $r = .12$ ). By 30 min AVP correlation with SAP change was non-existent ( $r = .05$ ) while a strong positive correlation between osmolality and serum AVP was found ( $r = .87$ ). We conclude that the biphasic shape of the fetal AVP response curve to a single H represents a dual response, the first phase triggered mainly by falling SAP and the second phase by increased serum osmolality.

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THE RELATIVE ROLE OF ANAEROBIC AND LOWERED METABOLISM IN NEONATAL ANOXIA TOLERANCE. Rolf R. Engel. Dept. of Pediatrics, University of Minnesota, Minneapolis.

The energy metabolism of newborn dogs subjected to anoxia was investigated by simultaneous direct and indirect calorimetry before, during and after anoxic episodes. In all 12 experiments the decrease in rectal temperature, heat loss, calculated heat production and post anoxic oxygen consumption provided incontrovertible evidence for a significant decrease in the rate of energy turnover during anoxia. With 9 or more minutes of anoxia at 29°C ambient temperature there was at least a 50% decrease in the rate of heat production. During longer anoxic intervals of 16 minutes at 20°C, heat production decreased to 80% of control values, and yet complete recovery occurred.

The concept of an anoxic oxygen debt was extended to encompass situations with changing rates of heat production by defining an oxygen debt in terms of the difference between direct and indirect calorimetry. The oxygen debt incurred (anoxic heat production ranged from 250 to 770 cal/kg) and the oxygen debt paid back (excess of indirect calorimetry over direct calorimetry) during the recovery period agreed within 12% ( $r = 0.7$ ). Identical studies on newborn kittens, rabbits and rats confirmed that in neonatal anoxia a progressive decrease in the metabolic rate of more than 70% is compatible with survival.