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DOSE DEPENDANT EFFECTS OF SURFACTANT ON LUNG MECHANICS. Haruo Maeta, Tetsuro Fujiwara, Mineo Konishi, Shinichi Asakura (Spon. by D. Vidyasagar). Department of Pediatrics, University of Iwate, Morioka, Japan.

Although exogenous surfactant replacement was proven to improve lung mechanics in clinical HMD (Fujiwara et.al. TA), optimal concentration and dose were not known. We studied the effect of different concentrations and quantity of TA in premature rabbits before first breath. Group A was treated with fixed lipid quantity, but variable TA concentration. Group B was treated with fixed concentration, but variable lipid quantity. We measured P-V curve (P-V) and lung-thorax compliance (CL) at 5 mg/ml to 40 mg/ml of concentration and 25 µg to 400 µg of quantity. Group A P-V curve data is given below. (Mean ± S.E.). In

Quan.Conc.	200 µg		400 µg		800 µg	
	n	*P5(ml/kg)	n	*P5(ml/kg)	n	*P5(ml/kg)
5 mg/ml	6	16.6±2.6	9	15.7±3.2		
10 mg/ml	11	21.8±2.6	11	30.5±4.3	9	50.5±3.5
20 mg/ml	7	22.8±6.2	11	39.0±4.1	9	49.6±4.7
40 mg/ml	14	22.7±1.8	13	36.5±2.5	21	46.8±4.1

Group A, when lipid quantity was kept constant the variable concentration 10 mg/ml to 40 mg/ml of TA did not change the P-V curve and the CL. However when concentration of TA dropped to 5 mg/ml, the P-V curve and the CL changed adversely ($p<0.02$). Group B P-V curve and CL improved to maximum at 800 µg irrespective of concentrations. Further, the lipid quantity of 800 µg to 4000 µg had no further beneficial or adverse effect. We conclude 10 to 40 mg/ml of TA concentration,and lipid quanity of 800 µg to 4000 µg will have optimal effect on P-V curve and CL when instilled before the first breath.(*P5=5 cmH2O distending pr.).

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EFFECT OF CAFFEINE EXPOSURE ON FETAL GROWTH IN THE RABBIT. Susan H. Mercik, Bruce R. Dorrbecker, Paul A. Kramer and John R. Raye. Univ. of Connecticut Health Center, School of Pharmacy and Dept. of Pediatrics, Farmington.

High doses of caffeine (C) have been reported to be teratogenic in animals and persistent behavioral effects have been seen in the offspring of rodents fed C during pregnancy. We have characterized methylxanthine exposure and effects on fertility and fetal growth resulting from continuous prenatal infusion of C at doses comparable to human dietary intake in the rabbit. The rabbit was chosen for its similarities to the human in metabolism of C. 26 rabbits were administered C during gestation at rates of 0, 10 or 20 mg/kg/day via an implanted infusion pump. Does were sacrificed at 10, 20 or 29 days, and amniotic fluid, fetal CSF, plasma and gastric fluid were collected. Fluids were analyzed for C and its major metabolite paraxanthine (P), and fertility and fetal growth were assessed. P and C were homogeneously distributed in fetal fluids. Mean amniotic fluid to maternal plasma concentration ratios were 0.4 and 0.6 for P and C, respectively, increasing to 0.7 and 0.9 by the end of gestation. Methylxanthine exposure did not affect pregnancy rate, litter size or fetal weight. Length, brain weight and liver weight at 29 days were not significantly different ($p>0.1$). We have demonstrated that prenatal administration of C to rabbits results in significant fetal exposure to both C and P. This exposure at clinically relevant levels did not lead to structural teratology or adversely affect fertility or fetal growth. The potential for long-term alterations in behavior (behavioral teratology), however, remains to be defined by studies now in progress.

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BRAIN PHENOBARBITAL (PB) CHANGES DURING SEIZURES (S) IN PIGLETS. Pierre MONIN[1], Martine CLOZEL[1], Paul VERT[1], Jean Luc DAVAL[1], Paolo L. MORSELLI[2], Catherine DUBRUC[2] (Spon. by M. DELIVORIA-PAPADOPOULOS). 1. Centre Rech. Biol. Dev. Humain, Université de Nancy I - 2. LERS Synthelabo, Paris - FRANCE.

During S, brain acidosis often associated to blood alkalosis (1) lead to a rise in blood-brain $[H^+]$ gradient ($G[H^+]$). According to the pH partition hypothesis PB should be released from brain tissue. To test this hypothesis 11 piglets less than 10 days are studied (mean weight ± 1 SD : 1.7 ± 0.6 kg) 6 to 12 hours after an IP dose of 10 mg/kg of PB. S are induced by pentylen tetrazol (P-100 mg/kg, n=4) or bicuculline (B-0.6 ± 1.2 mg/kg, n=7) in spontaneously breathing anesthetized animals (urethan 12.5 % sol, 15 ml/kg), PaO_2, $PaCO_2$, pHa, brain tissue pH (Roche electrode), blood and brain PB concentrations are measured. S lasted for 3 to 17 min. Mean changes are as follows :

	pHa	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	$G[H^+]$ (nmol/l)	PB art. µg/ml	Brain PB µg/ml
Before S	7.45*	36±5**	76±9**	57±20**	9.6±3.0*	7.9±3.9*
During S	7.43	26±5	96±10	96±38	9.1±3.4	8.5±4.4

During S, the brain/arterial PB ratio (b/a) rises from 0.83 ± 0.18 to 1.03 ± 0.30 (m ± 1 SD). It is > 1 in one case before S (1.08) and in 7 cases during S ($X^2 = 7.0$, $p < 0.01$). This suggest an unexpected PB intrusion into the brain during S which could be related to an opening of the blood brain barrier (BBB) as suggested by 1) the correlation between b/a and $\Delta G[H^+]$ ($r=0.67$, $p < 0.05$) and 2) the trend towards a correlation between brain PB and brain $[H^+]$ changes during S ($r=0.61$, ns). During S, higher is brain acidosis higher might be the BBB opening and the PB shift into the brain. 1. P. MONIN et al, Pediatr. Res., 1979, 13 : 527, *ns, **$p < 0.01$.

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PROTEIN PHOSPHORYLATION BY NONCYCLIC SECOND MESSENGERS IN HUMAN PLACENTA. John J. Moore (Spon. by J. Schrefer), CWRU Sch. Med., Metro Gen Hosp., Depts. Pediatrics and OB/GYN., Cleveland

The existence and extent of regulation of human placental function by maternal or fetal hormones remains undetermined. Protein phosphorylation (PP) activated by intracellular second messenger stimulation of specific protein kinases is the final event of many hormone initiated cascade systems. PP was investigated in human placental cytosol using [32]P-ATP in the presence and absence of known and postulated second messengers: cAMP, cGMP, Calcium and Polyamines. PP was assessed by SDS polyacrylamide gel electrophoresis and autoradiography and quantitated by densitometer scanning of the autoradiograph or counting of gels cut into 1mm slices. cAMP(10^{-6}) promoted incorporation (above basal $p<.01$) of .58,.47,.04 and .03 moles [32]P/mg cytosol protein into proteins of Mr= 70000, 58000, 52000 and 45000. Half maximal phosphorylation of the major 45000 Mr protein occurred with $1.1\pm.2\times10^{-7}$ M cAMP. cGMP activated PP of the same proteins as cAMP. However, half maximal activation required 10^{-5} M cGMP and cGMP PP was inhibited by cAMP dependent protein kinase inhibitor. Calcium activated PP of 4 proteins ($p<.02$) (Mr=67000, 58000, 20000, and 10000). Half maximal PP occurred with 10^{-7} M Ca. Calmodulin and phospholipids did not change Ca activated PP. The polyamine, spermine(10^{-3}M), promoted [32]P incorporation of $1.4\pm.02$ and $0.2\pm.01$ moles [32]P/mg cytosol protein into proteins of Mr=105000 and 55000.($p<.001$) Half maximal = $2.7\pm1.2\times10^{-4}$M spermine. (Other polyamines showed the potency order spermine>>spermidine> putrescine. cAMP and Ca had no effect upon PP by the other second messengers, however, spermine inhibited both cAMP ($IC50=5\times10^{-5}$M spermine) and Ca activated PP. The presence of 2 sets of phosphoproteins specifically activated by distinct second messengers supports the hypothesis that human placental function may be partially regulated by maternal or fetal hormones.

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COMPARISON OF SHORT TERM VS. LONG TERM RITODRINE EXPOSURE. M. N. Musci Jr., S. Abbasi, T. A. Losure, and R. Bolognase (Sponsored by L. Johnson), Children's Hosp. of Phila., Div. of Neonatology; Univ. of PA, Sch. of Med., Dept. of Ped. and Ob/Gyn., Pennsylvania Hospital, Phila., PA. Ritodrine hydrochloride as a tocolytic agent is gaining widespread acceptance in the USA after over a decade of use in Europe. Records were reviewed during the initial year of ritodrine use at Pennsylvania Hosp.(7/81 - 6/82). The protocol for administration was IV ritodrine followed by oral maintenance (usually 40-80 mg daily) until delivery. 55 of 68 women (81%) were treated to 35 weeks or greater with the following results:

Initiation of tx	N	$\bar{X}$ BW(gms)	$\bar{X}$ Gest.Age(wks) at delivery	$\bar{X}$ Duration(wks) of tx
<30wks	22	2893±424	38.4±2.0	13. ±5.3
≥30wks	25	3093±362	39.1±1.6	4.9±2.3
		N.S.	N.S.	
Duration of tx				
≤ 6wks	23	3047±394	38.7±1.8	3.7±1.6
> 6wks	27	3049±410	38.9±1.9	12.8±4.9
		N.S.	N.S.	

Neonatal side effects (hyperbilirubinemia, hypoglycemia, or respiratory distress) were not significantly increased in either group as compared to previous European reports, although our mean length of exposure is almost 4 times longer. This suggests that the current ritodrine regimen does not increase neonatal side effects and is effective in prolonging pregnancy. However, this may change as maintenance therapy is increased (up to 120 mg daily) in attempts to improve ritodrine's success.

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RITODRINE EXPOSURE IN UTERO: EFFECTS ON FETAL RATS M. N. Musci, Jr., P. Vasilenko, and S. Abbasi (sponsored by Lois Johnson), Children's Hosp. of Phila., Div. of Neonatology; Univ. of PA, Sch. of Med., Dept. of Ped., Pennsylvania Hosp., Phila, PA; Dept. of Med., Univ. of Med. and Dent. of NJ-Sch. of Osteo. Med., Camden, NJ. Beta-sympathomimetics used for tocolysis have been shown to cause changes in fetuses and neonates. Ritodrine (R) (5mg/kg, sc, q12h) was given to rats on days 10-19 of pregnancy. Control (C) rats received saline alone. On day 20 the animals were anesthesized and the fetuses were delivered via abdominal incision. (R) and (C) exhibited no significant differences in fetal or placental weight, placental glycogen content, or fetal and maternal blood glucose values. The following significant fetal results were obtained:

	Weights(gms) ± SEM		Glycogen(ug/mg) ± SEM	
	Heart	Liver	Heart	Liver
C (n=52)	22.0 ± 0.9	282.7 ± 13.6	23.8 ± 3.0	75.7 ± 3.9
R (n=68)	25.7 ± 0.9	279.2 ± 9.6	24.1 ± 3.3	84.8 ± 3.6
	$p<0.001$	N.S.	N.S.	$p<0.02$

Our findings that (R) causes cardiac muscle hypertrophy without affecting cardiac glycogen deposition are in agreement with reports of cardiovascular effects of the drug. The increase in liver glycogen content may indicate a hyperglycemic state which has also been linked to (R) therapy. Maternal heart weights and liver glycogen also increased in the (R) group, similar to the fetal changes. Unlike the fetuses, maternal cardiac glycogen content and pituitary weights were increased in the (R) group. These results suggest that cardiovascular and metabolic side effects be considered in infants born to mothers on (R).