0031-3998/84/1809-0854$02.00/0
PEDIATRIC RESEARCH

Vol. 18, No. 9, 1984
Printed in U.S.A.

Some Aspects of Maternal Metabolism Throughout Pregnancy in the Conscious Rabbit

MARC GILBERT, WILLIAM W. HAY, JR., ROBERT L. JOHNSON, AND FREDERICK C. BATTAGLIA

Division of Perinatal Medicine, Departments of Pediatrics and Obstetrics-Gynecology, University of Colorado School of Medicine, Denver, Colorado 80262

Summary

Studies of maternal metabolism during pregnancy have focused principally upon the latter half of gestation. However, maternal metabolic adaptations to pregnancy may occur at all stages of pregnancy. To study maternal metabolism throughout pregnancy, we developed a chronically catheterized rabbit model in which animals could be studied under conscious, stress-free conditions when nonpregnant and then serially throughout pregnancy.

Anesthesia produced marked hyperglycemia. In contrast, chronic catheterization and daily handling did not affect blood concentrations of glucose, lactate, ketone bodies, or free fatty acids, or food intake. Glucose concentration decreased with pregnancy to a value at term equal to 85% of the prepregnancy value. Lactate concentration rose significantly in the second half of pregnancy but changes in free fatty acids and ketoacid levels were not significant. These results are discussed from a comparative physiologic point of view, emphasizing the unique aspects of rabbit metabolism during pregnancy and the importance of performing such studies under conscious, stress-free conditions.

The impact of pregnancy upon maternal metabolism of carbohydrates and lipids has been studied in the rat (14, 20), guinea pigs (11, 37), and man (8, 18, 30). In these species, most studies were performed over the latter third of gestation. It is probable that the timing and the magnitude of maternal metabolic changes during pregnancy may be related to such factors as the growth rate of the fetus and the placenta, the fetal and placental mass and metabolic rate at different stages of pregnancy, and the maternal diet. In particular, animal species with a relatively short gestation that produce a large fetal to maternal mass ratio at term (*i.e.*, guinea pig, 0.50; rat, 0.17; and rabbit, 0.15) are of interest with regard to the maternal metabolic changes which occur during the entirety of gestation.

The majority of metabolic studies during pregnancy have involved surgical, anesthetic, and handling stress. In particular, in the rabbit there have been no studies describing maternal metabolism at any time of pregnancy under chronic, stress-free, steady state conditions. The present paper describes our results in developing techniques for chronic catheterization of rabbits prior to pregnancy, permitting metabolic studies in the conscious animal, free of surgical and anesthetic stress. Serial measurements of blood metabolite levels (glucose, lactate, free fatty acids, ketone bodies) and hormone levels (insulin and glucagon) were measured on the same animal before pregnancy and throughout pregnancy. These data provide an additional dimension for interspecies comparisons of the effects of pregnancy upon maternal metabolism including data for the very earliest pregnancy stages.

Received November 30, 1982; accepted March 12, 1984.
Address reprint requests to William W. Hay, Jr., M.D., University of Colorado School of Medicine, Box B195, Department of Pediatrics, 4200 East Ninth Avenue, Denver, CO 80262.
This work was supported by National Institutes of Health Program Grant HD00781. W. W. H., Jr. is the recipient of a Special Emphasis Research Career Award (Diabetes Mellitus: Pediatric Aspects), National Institutes of Health, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases-National Institute of Child Health and Human Development. R. L. J. was supported by National Institutes of Health Training Grant HD07186.

MATERIALS AND METHODS

Nonpregnant New Zealand White rabbits were obtained from a commercial breeder. Animals were housed in stainless steel cages and fed *ad libitum* a solid rabbit diet (Purina Rabbit Chow). The food intake was determined gravimetrically each morning.

Surgery was carried out on nonpregnant rabbits. Animals were anesthetized with ketamine hydrochloride (35 mg·kg^{-1} IM) and xylazine hydrochloride (6 mg·kg^{-1} IM). Using sterile technique, a 20-gauge polyvinyl catheter was introduced into the right carotid artery and advanced into the left ventricle. Another polyvinyl catheter of the same size was introduced into the contralateral jugular vein. Catheters were tied in place and secured with tissue adhesive (No. 910 Eastman Kodak). The catheters were tunneled under the skin to exit into a capped plastic cap sutured to the back of the neck (37). Catheters were filled with a heparin solution (200 units/ml of 0.9% NaCl) and were flushed with this solution every 3 days. The catheters were kept patent for withdrawal for at least 5 weeks. The arterial catheter was used to draw blood samples and the venous catheter was used for any infusions.

The rabbits were allowed to recover from surgery for at least 2 days. A week later they were bred by artificial insemination (4). Females were injected intravenously with 5 mg of pituitary luteinizing hormone (Armour-Baldwin Laboratories, Omaha, NE) (25), and immediately thereafter 0.5 ml of freshly collected semen from a buck was injected into the vagina.

The rabbits were handled daily, in a gentle manner, by the same two persons. The rabbits were kept in standard stainless steel cages which were darkened by drapes except at the front. Studies and sampling were performed with the rabbit in this same cage, or, after adaptation, in an 8 × 8 × 16 inch plastic tray open at the top. No attempt was made to restrain the rabbits. These careful methods of handling were necessary to ensure stability of the rabbit for chronic, stress-free studies. In this regard, the rabbit poses a unique challenge for careful chronic handling quite unlike the guinea pig which tolerates movement and handling without significant difficulty (37).

Arterial blood samples were obtained every 2 to 3 days between 0900 and 1000 h for substrate and hormone determinations. Whole blood glucose concentration was measured with a glucose oxidase method (16). Concentrations of lactate, acetoacetate, and

β-hydroxybutyrate in whole blood were determined by standard enzymatic methods after perchloric acid precipitation (12). Serum free fatty acids were determined by the method of Ho (15).

Immunoreactive insulin was measured with a heterologous immunoassay system as previously described (19). The standard hormone was crystalline rabbit insulin (22.7 U/mg; batch K 13369) supplied by Novo Industry, Copenhagen, Denmark. Immunoreactive glucagon was assayed using specific antibody (30K) for pancreatic glucagon (1). For each hormonal determination, all plasma samples were run in the same assay. The intra-assay variation for replicate determinations of the same sample was 10 ± 1% (SEM) for both hormones.

Statistics. Multiple values of a given measurement for one animal were averaged for that animal before comparison among animals. Results are expressed as mean ± SEM. Calculations of statistical significance of differences between groups were performed using Student's *t* test for unpaired data. Linear regressions of substrate concentrations *versus* gestational age were calculated by the least squares method. Mean substrate values for each animal on each sampling day were averaged and the mean value for a given substrate among animals was used for calculating the regression equation and the correlation coefficient.

RESULTS

Studies on Nonpregnant Rabbits. Effects of anesthesia on blood glucose concentration. Most studies of substrate concentrations in small animals have been carried out with animals under anesthesia and/or surgical stress. In order to assess the impact of these surgical procedures and anesthesia upon blood glucose concentration, four conscious animals (three nonpregnant and one pregnant on day 28) with indwelling catheters were studied in the following manner. Glucose concentration was first measured on a conscious animal that had been operated upon previously for the placement of catheters (Fig. 1). The rabbits were then anesthetizied as already described. Fifteen minutes later, just prior to surgery, another blood sample was drawn. Surgery was then performed similar to that for catheter insertion (skin incision, muscle manipulation, jugular vein and carotid artery isolation by blunt dissection). Blood samples were obtained every 15 min for the next 60 min.

For the first 15 min following anesthetic administration, all rabbits increased their glucose concentration by about 50% and sustained this level for 45 min. Surgery itself appeared to have little additional effect on blood glucose concentration. However, after surgery, two rabbits sustained their hyperglycemia for 60 min.

Effects of long term catheter implantation on substrate concentration. Data in Table 1 show that chronic catheterization in six nonpregnant, female rabbits for 1 month did not affect the concentration of glucose, lactate, acetoacetate, and free fatty acids as well as food intake. There was no relationship between substrate concentration and the duration of gestation ($p > 0.1$).

Studies on Pregnant Rabbits. Identical techniques were applied to study pregnant rabbits during full pregnancy (30 days) to determine the effects of pregnancy upon substrate and hormone levels. Seven rabbits were studied before pregnancy and throughout pregnancy.

Food intake and maternal weight. Over the first 25 days of pregnancy, food intake remained constant averaging 40 $g \cdot day^{-1}$ kg^{-1}, similar to that measured in the group of six nonpregnant rabbits. Five of the seven rabbits reduced their food intake by about 15% for the last 4 days of gestation (Fig. 2). Food intake was also monitored for 24 h at 4-h intervals in two groups of pregnant rabbits (Fig. 3). The first two groups with gestational ages of 8–14 days (five rabbits) and 22 days (three rabbits), respectively, showed that the food intake per animal (12 $g \cdot 4\ h^{-1}$) remained almost constant from 0430 to 1230 and then rose progressively until 0030 (35 ± 5 $g \cdot 4\ h^{-1}$) when it was about 3 times higher than morning values. On day 29 of gestation (second group, four rabbits), the animals ate less over a 24-h period and showed less of an increase of food intake during the evening.

The rabbits' weight ranged from 3.5–4.0 kg. The maternal weight gain was negligible throughout pregnancy ($r = 0.030$; $p > 0.1$).

Substrate Concentrations. Blood glucose. Blood glucose con-

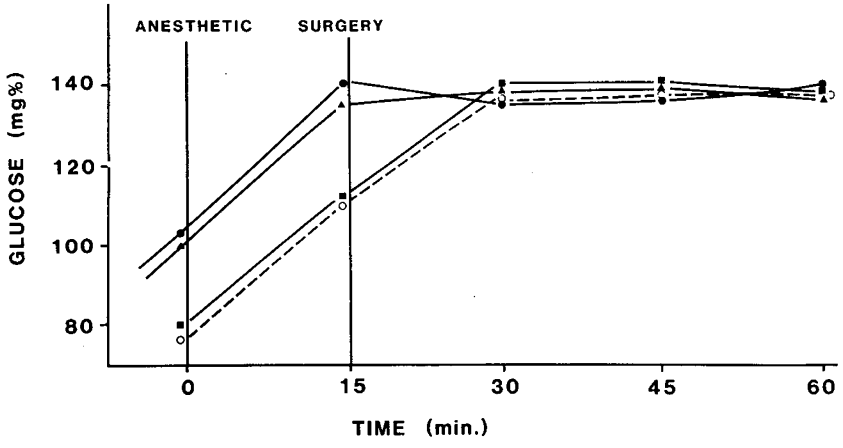

Fig. 1. Effect of ketamine-xylazine anesthesia and surgery on blood glucose concentration in four conscious rabbits: three nonpregnant (——), and one pregnant on day 29 of gestation (- - -).

Table 1. *30-Day studies in six nonpregnant, female rabbits ($\bar{x}$ ± SEM)*

	Metabolic levels	Regression line	*r*	*n*	*p*
Food intake					
$g \cdot day^{-1}\ kg^{-1}$	39.0 ± 0.9	−0.0638x + 39.81	0.047	148	>0.1
$g \cdot day^{-1}\ animal^{-1}$	132.2 ± 3.0	−0.0104x + 134.9	0.025	148	>0.1
Glucose (mg/dl)	92.6 ± 1.0	+0.0539x + 91.84	0.052	58	>0.1
Lactate (mM)	0.819 ± 0.135	+7.37x + 0.721	0.066	31	>0.1
Acetoacetate	0.065 ± 0.071	+0.16x + 0.062	0.025	37	>0.1
Free fatty acids (μM)	519.1 ± 40.8	+2.413x + 486.8	0.061	48	>0.1

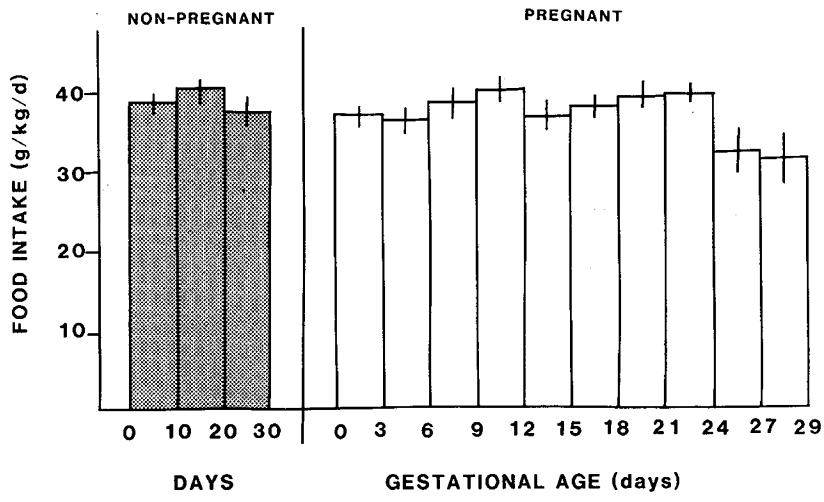

Fig. 2. Food intake in six nonpregnant and seven pregnant rabbits over 4 weeks ($g \cdot kg^{-1}$ day^{-1}; mean ± SEM). Food intake decreased during the last week of pregnancy (days 24 to 29) in five of the seven pregnant rabbits averaging 15% less than in the 1st week of pregnancy.

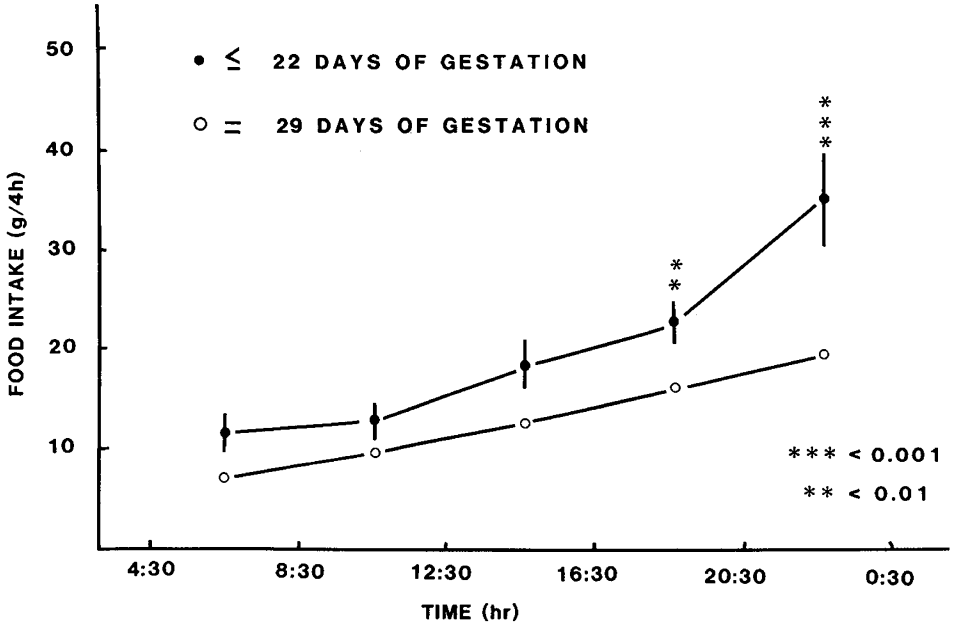

Fig. 3. Food intake, mean ± SEM, for pregnant rabbits over 24 h. The late evening food intake is significantly greater than the morning food intake (**, $p < 0.01$ from 1630–2030 *versus* 0430–0830; ***, $p < 0.001$, from 2030–0030 *versus* 0430–0830).

centration averaged 94 ± 1.6 mg/dl in the nonpregnant state. In pregnant animals, there was a progressive decline in glucose concentration with advancing gestation ($y = -0.54x + 93.4$; $r = 0.64$; $p < 0.001$). A significant change in glucose level (88 ± 15 mg/dl; $p < 0.02$) occurred as early as 8 days of gestation when compared with the nonpregnancy value (Fig. 4). On day 29, the glucose concentration averaged 79.5 ± 2.7 mg/dl, equal to 85% of the prepregnancy level (significantly less than the prepregnancy value; $p < 0.01$).

Lactate, free fatty acids, and ketone bodies. For the first half of gestation, the mean concentrations of lactate and free fatty acids (Fig. 5*A*) remained unchanged and similar to the nonpregnant levels. For lactate, this plateau was followed by a progressive increase in concentration until day 27. At term, the mean value averaged nearly 3-fold higher than on day 1 ($p < 0.05$). A progressive, slight rise in fatty acid concentration occurred from days 25 to 29, but the final values were not significantly different from those in early pregnancy. The concentrations of acetoacetate and β-hydroxybutyrate (Fig. 5*B*) did not change throughout pregnancy.

Insulin and glucagon concentrations. Plasma insulin concentration remained unchanged (9–10 μU/ml) during pregnancy (Fig. 6). By contrast, the mean plasma glucagon concentration tended to decrease for the first two-thirds of gestation but the change was not statistically significant. In the last third of pregnancy, the glucagon concentration declined progressively until term. On day 29, the mean value (167 ± 8 pg/ml) was approximately one-half that of the concentration on day 4 (279 ± 12 pg/ml; $p < 0.001$).

DISCUSSION

To our knowledge, this is the first longitudinal study throughout pregnancy carried out in a conscious, pregnant small mammal. In rats, which have been most extensively studied, there are no metabolic data from conception to term. In addition, most of the data in rats have been obtained over the latter half of gestation using a variety of techniques [by decapitation (9, 27); under anesthesia (14, 20, 33); in awake animals (39); and most recently, in chronically chatheterized animals (10)]. These studies have produced quite variable results. Because of these problems, the first goal of the present studies was to establish a stress-free

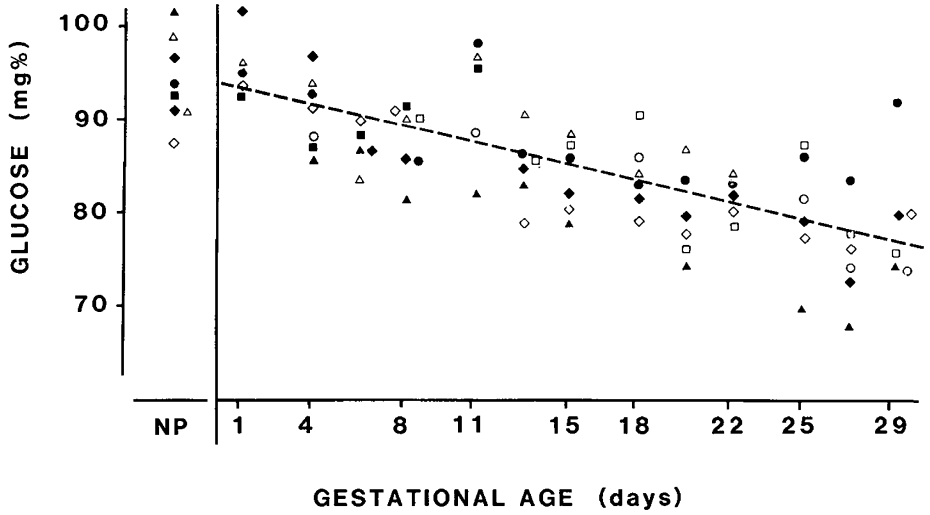

Fig. 4. Blood glucose concentrations in seven pregnant rabbits sampled between 0800 and 1100 every 3rd to 4th day of pregnancy. The progressive decline in glucose concentration ($y = -0.54x + 93.4$) is highly significant ($r = 0.64$; $p < 0.001$).

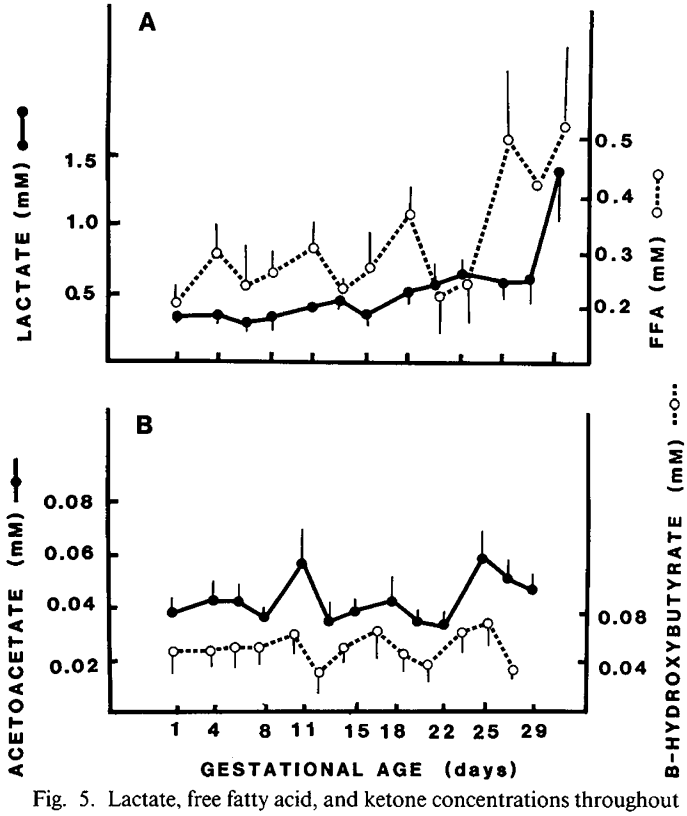

Fig. 5. Lactate, free fatty acid, and ketone concentrations throughout pregnancy (mean ± SEM). On day 29, blood lactate concentration (*A*) was 3-fold higher than the prepregnant value ($p < 0.005$). In late gestation, serum free fatty acid (*FFA*) values (*A*) were not significantly greater than the prepregnancy values ($p > 0.1$). Ketone body levels (*B*) remained unchanged throughout pregnancy.

small animal model that could be studied over the entire length of gestation. The present studies demonstrate that chronic catheterization and daily handling did not affect blood concentrations of metabolic substrates. Similar results have been observed with a chronically catheterized pregnant guinea pig model. In contrast, the present study clearly demonstrates changes in glucose concentrations induced by anesthetic stress. In both guinea pigs and sheep, substrate concentration changes induced by such stress have been well documented (2, 37). Thus, the choice of a chronic, conscious, stress-free animal preparation is essential to answer questions of maternal metabolic changes induced by pregnancy.

During pregnancy, the mother must meet both its own and the nutritional requirements of the conceptus. To accomplish this goal, one might expect that maternal food intake would increase. In rats (10, 20, 38) and guinea pigs (37), the absolute values of food intake over the last half of gestation increased by 25 and 50%, respectively. In the present study, the rabbits did not increase food intake throughout pregnancy (Fig. 2) in agreement with previous data (6, 21, 42). In fact, food intake was reduced by about 15% for the last 4 days of gestation, similar to the rat in which the food intake drops by 15–20% 2 days before term (10, 20, 38).

The present study also demonstrates that the bulk of the rabbit's daily food intake is ingested during the night. In rats, Strubbe and Gorissen (38) also found that feeding activity was primarily nocturnal. Thus, differences in blood substrate concentrations among species may simply reflect differences in feeding behavior and sampling time.

At term in the guinea pig, the rat, and man, the mother has increased her total weight by about 60% (37), 30% (2, 20), and 16% (31), respectively. In guinea pigs 80–90% of the total body weight gain can be accounted for as fetal mass (37). In the rat, for the initial two-thirds of gestation, the maternal body weight rises by 10% (38) corresponding to an increase in fat storage (21). For the remaining third of pregnancy, maternal weight increases by about 20% (20, 38), and this weight gain can be ascribed to the growing fetal mass. The present study demonstrates that in the rabbit at term, when the total fetal mass equals about 10–15% of the prepregnant weight, nonuterine maternal tissues must have lost weight since maternal body weight did not increase significantly during gestation. These results are in agreement with those reported previously (21).

The present study demonstrates that neither an increased food intake nor an increased maternal weight can be considered a uniform characteristic of mammalian reproduction.

The second goal of these studies was to observe the effects of pregnancy on circulating substrate concentrations from conception to term. In the present study, the rabbits' blood glucose concentration decreased progressively from the 1st week of pregnancy until term (Fig. 4). In anesthetized rats, several studies have observed a progressive decline of the blood glucose concentration over the latter half of gestation (14, 20, 23). By contrast, in conscious pregnant rats, a constant glucose concentration was found from midgestation until term (10). In conscious, pregnant guinea pigs, Sparks *et al.* (37) observed the glucose concentration to fall with advancing gestation. A longitudinal study has described a progressive fall in blood glucose concentration throughout human pregnancy (41) and in late human pregnancy, following an overnight fast (3, 34, 41) or in the postabsorptive state (5,

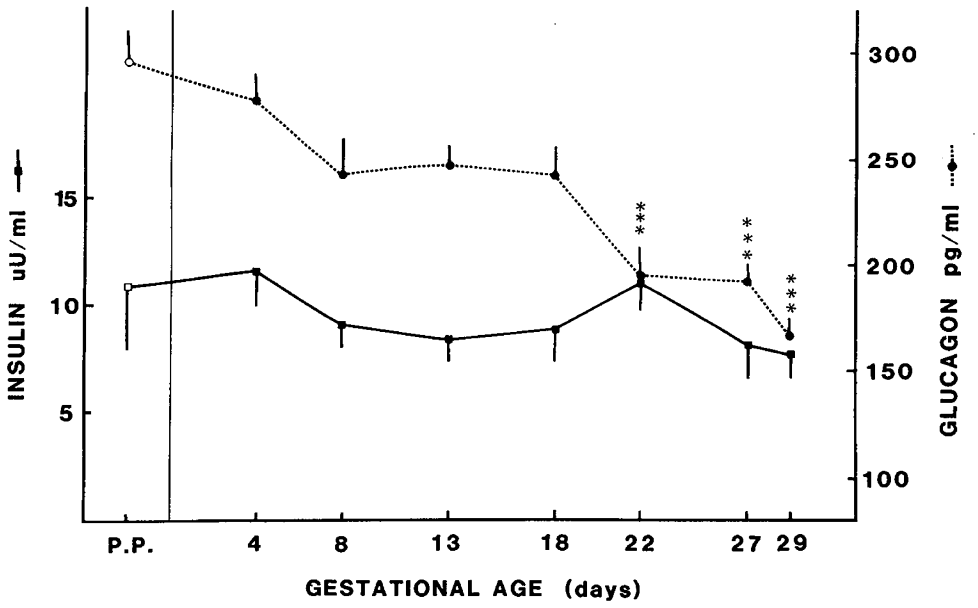

Fig. 6. Plasma insulin and glucagon concentration throughout pregnancy (mean ± SEM). On days 22 and 27, the glucagon level was significantly lower ($p < 0.01$) than on any previous sample day. The average glucagon concentration on day 29 (167 ± 8 pg/ml) was about one-half that of the average prepregnancy value of 295 ± 15 pg/ml ($p < 0.001$). Plasma insulin concentration did not change during pregnancy ($p > 0.1$).

41), blood glucose concentration has been found to be lower than in the nonpregnant state.

The reasons for the fall in glucose concentration with advancing gestation are not known although pancreatic glucoregulatory hormones have been implicated in producing this phenomenon. At term in pregnant rats, plasma insulin levels are higher (14, 20, 32) or unchanged (22) compared to those of nonpregnant animals. In pregnant women, prepartum values are slightly higher than postpartum values (28). In the same set of experiments, glucagon levels rose by 40% in late gestation in rats (32) but did not change in pregnant women (28). In the rabbits in the present study, plasma insulin concentration remained unchanged throughout pregnancy. In contrast, plasma glucagon progressively declined over the period studied, the largest decrease occurring during the last third of gestation. The lowered plasma glucagon levels could be explained by decreased glucagon stores in the pancreas since a degranulation of α cells occurs in pregnant rabbits (24). The decline in the glucagon levels without concomitant changes in insulin levels produced an increase in the insulin:glucagon ratio. An increased insulin:glucagon ratio might affect glucose concentration by decreasing hepatic glucose production. It is well known that the rat of hepatic glucose production is directly related to the insulin:glucagon ratio in nonpregnant dogs and humans (40). In this regard, Hay *et al.* (13) have shown a constant weight-specific glucose utilization rate throughout pregnancy in chronically catheterized, conscious rabbits. Similar results have been obtained for the pregnant rat (23) in which additional evidence supports a decreased insulin sensitivity in late gestation for the liver (22).

The present study does not show a marked rise of free fatty acid concentration during the rabbits' pregnancy until 4–5 days before term, when the food intake is also reduced. The absence of a change in ketone body concentrtions near term may suggest only a moderate rate of lipolysis, although a simultaneous increase of ketone body utilization may have masked an elevation in concentration. In rats, plasma free fatty acid concentrations rise progressively from midgestation until term (10, 20). There are conflicting data for other species: the levels of fatty acids during pregnancy have been reported unchanged in chronically catheterized guinea pigs (37), and in humans (7, 29) while there have been reported increases in acutely stressed guinea pigs (17) and in humans (26).

The present studies also confirm the rise of blood lactate with gestation, similar to previous reports in rats (10). Causative factors are not yet established although recent studies have demonstrated a net placental production of lactate in the sheep (35) and in the uterus of the guinea pig and rabbit (36). Hence, the placental mass may be a site of high lactate production contributing to the rise of maternal lactate concentration.

REFERENCES

1. Assan R, Tchobroutsky G, Derot M 1971 Glucagon radioimmunoassay: technical problem and recent state. Horm. Metab. Res. (Suppl 1) 5:82
2. Battaglia FC 1979 Umbilical uptake of substrates and their role in fetal metabolism. In: Visser HKA (ed) Nutrition and Metabolism of the Fetus and Infant. Martinus Nijhoff Publishers, The Hague, pp 83–91
3. Bleicher SJ, O'Sullivan JB, Freinkel N 1964 Carbohydrate metabolism in pregnancy. V. The interrelations of glucose, insulin and free-fatty acids in late pregnancy and post partum. N Engl J Med 271:866
4. Bredderman BJ, Fotte RH, Yassen AM 1964 An improved artificial vagina for collecting rabbit semen. J Reprod Fert 7:401
5. Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J, Yen SSC 1980 The 24 hour excursion and diurnal rhythm of glucose, insulin and C-peptides in normal pregnancy. Am J Obstet Gynecol 136:483
6. Edson JL, Hudson DG, Hull D 1975 Evidence for increased fatty acid transfer across the placenta during a maternal fast in rabbits. Biol Neonate 27:50
7. Edstrom K, Perrson B, Cerasi E, Luft R 1975 Patterns of free-fatty acids, glycerol, D-beta hydroxybutyrate and insulin in pregnant women and their newborn infants. Acta Obstet Gynecol Scand 54:347
8. Freinkel N, Metzger BE 1975 Some considerations of fuel economy in the fed state during late human pregnancy. In: Davalos-Camerini RA, Cole HS (eds) Early Diabetes in Early Life. Academic Press Inc., New York, pp 289–301
9. Furner RL, Neville ED, Talarico KS, Feller DD 1972 Effects of pentobarbital on plasma glucose and free-fatty acids in the rat. Proc Soc Exp Biol Med 139:231
10. Gilbert M, Pegorier JP 1981 Substrate concentration changes during pregnancy in the conscious rat. J Dev Physiol 3:343
11. Gilbert M, Sparks JW, Girard J, Battaglia FC 1982 Glucose turnover rate during pregnancy in the conscious guinea pig. Pediatr Res 16:310
12. Girard JR, Chendet GS, Marliss EB, Kervran A, Rieutort M, Assan R 1973 Fuels, hormones and liver metabolism at term and during the early postnatal period in the rat. J Clin Invest 52:3190
13. Hay WW Jr, Gilbert M, Johnson RL, Battaglia FC 1984 Glucose turnover rates in chronically catheterized nonpregnant and pregnant rabbits. Pediatr Res 18:276
14. Herrera E, Knopp RH, Freinkel N 1969 Carbohydrate metabolism in Pregnancy. VI. Plasma fuels, insulin, liver composition, gluconeogenesis and nitrogen metabolism during late gestation in the fed and fasted rat. J Clin Invest 48:2260
15. Ho RJ 1970 Radiochemical assay of long-chain fatty acids using ^{63}Ni as tracer. Anal Biochem 36:105
16. Huggett ASG, Nixon DA 1957 Use of glucose oxidase peroxidase and *o*-dianisidine in the determination of blood and urinary glucose. Lancet 2:368
17. Jones CT 1976 Lipid metabolism and mobilization in the guinea pig during

pregnancy. Biochem J 156:357
18. Kalkhoff RK, Hissebah AM, Hak-Joong K 1978 Carbohydrate and lipid metabolism during normal pregnancy: relationship to gestational hormone action. Sem Perinatol 2:291
19. Kervran A, Rieutort M, Guillaume M 1976 A simultaneous radioimmunoassay for growth hormone and insulin in the plasma of rats and rabbits. Diabetes Metab 2:67
20. Knopp RH, Saudek CD, Arky RA, O'Sullivan JB 1973 Two phases of adipose tissue metabolism in pregnancy: maternal adaptation for fetal growth. Endocrinology 92:984
21. Lebas F 1975 Etude chez la lapine de l'influence du niveau d'alimentation durant la gestation. Ann Zootech. 24:267
22. Leturque A, Ferre P, Satabin P, Kervran A, Girard J 1980 *In vivo* insulin resistance during pregnancy in the rat. Diabetologia 19:521
23. Leturque A, Gilbert M, Girard J 1981 Glucose turnover during pregnancy in anesthetized post-absorptive rats. Biochem J 196:633
24. Lopez-Quijada C, Gomez Acebo J, Candela JLR 1967 Decrease in the insulin of rabbit pancreas in late pregnancy. Diabetologia 3:435
25. Maurer RR, Hunt WL, Foote RH 1968 Repeated superovulation following administration of exogenous gonadotrophins in Dutch-belted rabbits. J Reprod Fert 15:93
26. McDonald-Gibson RG, Young M, Hytten FE 1975 Changes in plasma esterified fatty acids and serum glycerol in pregnancy. Br J Obstet Gynecol 82:460
27. Metzger BE, Hare JW, Freinkel N 1971 Carbohydrate metabolism in pregnancy. IX. Plasma levels of gluconeogenic fuels during fasting in the rat. J Clin Endocrinol Metab 33:869
28. Metzger BE, Unger RH, Freinkel N 1977 Carbohydrate metabolism in pregnancy. XIV. Relationships between circulating glucagon, insulin, glucose and amino acids in response to a "mixed meal" in late pregnancy. Metabolism 26:151
29. Perrson B, Lunell NO 1975 Metabolic control in diabetic pregnancy. Am J Obstet Gynecol 122:737
30. Phelps RL, Metzger BE, Freinkel N 1981 Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free-fatty acids, triglycerides, cholesterol and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 140:730
31. Pitkin RM 1977 Obstetrics and gynecology. In: Schneider HA, Anderson CE, Coursin DB (eds) Nutritional Support of Medical Practice. Harper and Row, New York, pp 407–421
32. Saudek CD, Finkowski M, Knopp RH 1975 Plasma glucagon and insulin in rat pregnancy. Roles in glucose homeostasis. J Clin Invest 55:180
33. Scow RO, Chernick SS, Brinley MS 1964 Hyperlipemia and ketosis in the pregnant rat. Am J Physiol 206:796
34. Silverstone FA, Solomon E, Rubricius J 1961 The rapid intravenous glucose tolerance test in pregnancy. J Clin Invest 40:2180
35. Sparks JW, Hay WW Jr, Meschia G, Battaglia FC 1982 Lactate production and utilization rates in the lamb fetus *in vivo*. J Clin Invest 70:179
36. Sparks JW, Johnson R, Block S, Hay WW Jr, Meyers S, Meschia G, Battaglia FC 1982 Comparative physiology of the pregnant chronically catheterized sheep, guinea pig and rabbit. Fed Proc 41:1376 (Abstr 6463)
37. Sparks JW, Pegorier JP, Girard J, Battaglia FC 1981 Substrate concentration changes during pregnancy in the guinea pig studied under unstressed steady state conditions. Pediatr Res 15:1340
38. Strubbe JH, Gorissen J 1980 Meal patterning in the lactating rat. Physiol Behav 25:775
39. Sutter-Dub MT, Leclercq R, Felix JM, Jacquot R, Sutter BCJ 1973 Serum progesterone and immunoreactive insulin levels in the pregnant rat. Horm Metab Res 5:18
40. Unger R, Orci L 1981 Glucogon and the A cell. Physiology and pathophysiology. N Engl J Med 304:1518
41. Victor AL 1974 Normal blood sugar variation during pregnancy. Acta Obstet Gynecol Scand 53:37
42. Zilversmit DB, Hughes LB, Remington M 1972 Hypolipidemic effect of pregnancy in the rabbit. J Lipid Res 13:750

0031-3998/84/1809-0859$02.00/0
PEDIATRIC RESEARCH

Vol. 18, No. 9, 1984
Printed in U.S.A.

Vasodilators and Ventricular Septal Defect: Comparison of Prazosin, Minoxidil, and Hydralazine in a Chronic Lamb Model

MARK M. BOUCEK, RICHARD CHANG, AND DAVID P. SYNHORST

Department of Pediatrics, Division of Pediatric Cardiology, University of Utah College of Medicine and Primary Children's Medical Center, Salt Lake City, Utah 84132

Summary

The volume overloading of the left ventricle which results from left to right (L-R) shunting through a ventricular septal defect (VSD) may be reduced by pharmacologic agents which lower systemic vascular resistance (R_s) in excess of pulmonary arteriolar vascular resistance (R_{pa}). To study agents capable of decreasing the L-R shunt through systemic vasodilatation, we created a chronic lamb model with VSD and administered three vasodilators, prazosin (0.05 mg/kg), hydralazine (0.75 mg/kg), and minoxidil (0.25 mg/kg). Prazosin increased the R_{pa} while lowering R_s, resulting in an increase in R_{pa}/R_s by 43% ($p \leq 0.005$). Prazosin decreased the pulmonary flow ($\dot{Q}_p$) slightly, decreased L-R shunt by 16%, reduced the pulmonary to systemic flow ratio ($\dot{Q}_p/\dot{Q}_s$) by 22% ($p \leq 0.005$), and lowered the left atrial mean pressure ($\overline{LA}$) by 16% ($p \leq 0.005$) with no effect on heart rate. Hydralazine lowered the R_{pa} and R_s equally and thus did not change the R_{pa}/R_s or the volume of L-R shunt (7.6 *versus* 8.1 liters/min/m^2). No change in $\overline{LA}$ was seen with hydralazine but heart rate increased from 162 to 200/min ($p \leq 0.01$). Minoxidil did not change the L-R shunt (6.9 *versus* 6.8 liters/min/m^2) and, in general, produced effects intermediate between prazosin and hydralazine. The data support a selective systemic vasodilation with prazosin, a property not shared by either minoxidil or hydralazine, which results in a reduction of shunting and left ventricular volume overloading in lambs with VSD. Furthermore, since prazosin did not decrease the pulmonary resistance, the data indicate that the elevation in pulmonary resistance in lambs with VSD is not mediated by the α_1-adrenergic receptor.

Received July 25, 1983; accepted February 7, 1984.
Correspondence may be addressed to Mark M. Boucek, M.D., Division of Pediatric Cardiology, Room 2B-415, University of Utah College of Medicine, Salt Lake City, UT 84132.
This work was supported in part by United States Public Health Service Grants HL21203 and HL27802 and The Thrasher Research Fund.

Abbreviations

VSD, ventricular septal defect
R_{pa}, pulmonary arteriolar vascular resistance