Effect of DCA and Post DCA Hypertension Upon the Course of Pregnancy in the Rat.* (30497)

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Several workers have shown that desoxycorticosterone acetate together with an increased dietary intake of sodium chloride will produce hypertension in the rat(1,2). We have shown that an increase in the dietary intake of sodium chloride in partially nephrectomized dogs will produce hypertension and transient increases in sodium space, tissue pressure and blood volume(3,4). Masson *et al*(5,6) have found that a combination of vasopressor substances and salt and/or steroids like renin and DCA will produce an eclamptic-like syndrome in rats. Although pregnancy will cause the blood pressure to decrease when hypertension has been previously produced by a partial constriction of the renal artery(7), Page(1) found that pregnancy had no influence upon hypertension induced in rats by sodium chloride and DCA.

The effect of DCA and sodium chloride and post DCA hypertension on fetal and neonatal morbidity and on the weight changes in pregnant rats has not been reported previously. The present experiments were designed to study changes in weight, arterial pressure, proteinuria, and fetal and neonatal morbidity during pregnancy in rats made hypertensive by DCA and sodium chloride. Also, these parameters were followed during pregnancy in rats with post mineralocorticoid hypertension, *i.e.*, in rats bred after withdrawal of the DCA-sodium chloride regimen.

Materials and methods. Thirty-eight Holtzman albino rats were used. Arterial pressures were determined by the method described by Friedman and Freed(8). Urine protein concentration was measured by precipitation with sulfosalicylic acid; this was then compared spectrophotometrically to a solution of known protein concentration.

After establishing controls for arterial pressure and proteinuria, the left kidney was removed from 30 of the rats. Eight normal rats served as controls. Following a recovery period of 4 weeks the uninephrectomized rats were given daily injections of 4 mg/kg desoxycorticosterone acetate in Upjohn #98 vehicle. A 1% sodium chloride was substituted for their drinking water when DCA administration was begun. Twenty of the rats received the DCA and sodium chloride throughout the entire study. Ten of the rats received the DCA and sodium chloride for 8 weeks and were bred 25 days after withdrawal from the regimen. All animals in these groups were exposed to male rats for a period of 5 days. Eleven of the 20 rats receiving the DCA and sodium chloride became pregnant, 6 of the 10 post mineralocorticoid rats became pregnant, and all of the normal rats became pregnant.

The rats were weighed each day and arterial pressure was measured approximately 3 times each week. Proteinuria was determined twice each week.

Results. I. *Effect of pregnancy on animals receiving DOCA and sodium chloride.* The control arterial pressure was 117 mm Hg ± 13 S.D. prior to DOCA-sodium chloride administration. The arterial pressure rose to hypertensive levels within 2 weeks after the animals began receiving the DOCA and 1% sodium chloride and remained elevated throughout the study. The arterial pressure of the pregnant rats in this group at term was 181 mm Hg ± 22 S.D. and arterial pressure of the non-pregnant rats in this group during the same period was 170 mm Hg ± 19 S.D. (difference not statistically significant).

Pregnancy had no measurable effect on arterial pressure but there was a transient increase in proteinuria from 2.7 mg/24 hr ± 1.7 S.D. during the control period to 35.4 mg/24 hr ± 12 S.D. during the last 2 weeks of pregnancy. Protein excretion in the non-hypertensive rats rose from 2.1 mg/24 hr ± 1.9 S.D. prior to pregnancy to 5.9 mg/24 hr ± 3.0 S.D. during pregnancy. There was a

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TABLE I. Effect of Pregnancy on Normal and Hypertensive Rats.

	DCA + NaCl	Post DCA + NaCl	Control
No. of rats	20	10	8
No. pregnant	11	6	8
Avg No. per litter	10	7	11
% Born alive	66	75	100
Arterial pressure (3rd wk of pregnancy)	181.4	160.2	114.4
Convulsions	2	1	0

30% reduction in proteinuria in the hypertensive group following delivery. Two days prior to delivery 4 of the rats experienced a 10% to 16% increase in weight within a 24-hour period and 2 of them convulsed (Table I). No convulsions were observed in the hypertensive non-pregnant rats. There was an average of 10 rats per litter in this group (as compared to 11 rats per litter in the control group). However, only 66% of the offspring were born alive, and 100% of the offspring in the control group were born alive. It is noted also that the arterial pressure of the experimental group was 67 mm Hg higher than that of the control group during the third week of pregnancy. There was a 35% mortality rate among pregnant and non-pregnant adults during the period of study as compared to a zero mortality rate among the normal animals.

II. *Effect of pregnancy on post mineralocorticoid hypertension.* Table I also shows results obtained from 10 rats which were exposed to males 25 days after withdrawal from DOCA and 1% sodium chloride. There was a slight decrease in arterial pressure following withdrawal from the DOCA and sodium chloride regimen, but pregnancy had no effect on the course of the arterial pressure. Indeed the arterial pressure of this group of animals during pregnancy did not differ significantly from that of the non-pregnant rats which were treated similarly. The arterial pressure of this group during the third week of pregnancy was 160 mm Hg ± 12 S.D. There was also a 36.3% increase in proteinuria during the third week of pregnancy. There was an average of 7 rats per litter in this group (significantly less than the other two groups) and 75% of the offspring were alive at birth.

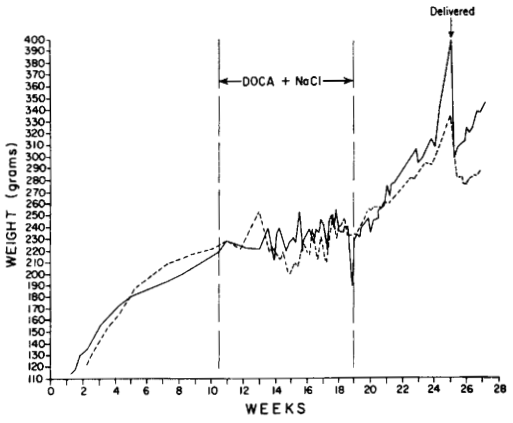

FIG. 1.

The curves in Fig. 1 show the changes in weight of 2 of the animals in this group. There was initially a progressive increase in weight. However, when the animals began receiving the DOCA and 1% sodium chloride their weight became unstable and remained unstable until the DOCA and sodium chloride was stopped.

After this regimen was withdrawn, their weights once again progressively increased. Two days prior to delivery the animal whose weight is represented by the solid line suddenly experienced a 12% increase in weight within a 24-hour period, convulsed, but subsequently delivered 12 living young. The rat whose weight is represented by the dotted line followed a course of pregnancy not unlike that of the control animals.

Discussion. While pregnancy had no effect on arterial pressure of rats which received DOCA and 1% sodium chloride nor on arterial pressure of rats which had post mineralocorticoid hypertension, proteinuria developed during the third week of pregnancy in both groups and subsequently decreased following delivery. In addition to causing a significant increase in proteinuria, the fluid balance was altered in some of the animals in each group as was evident from the excessive weight gain 24 to 48 hours prior to delivery. Page(1) earlier reported transient proteinuria in this type preparation and noted no change in blood pressure, nor in fluid balance. The system which maintains fluid balance during normal growth apparently becomes unstable in the animals during

administration of DOCA and sodium chloride as is evident from the varying weights during this period. Thus, pregnancy could conceivably result in a more pronounced instability in this system in some of the animals producing excessive weight gains and/or convulsions. We showed in a previous study(4), that fluid changes such as these could cause hypertension in the dog. An increase in arterial pressure was not observed in the present study during pregnancy although the animals were unable to maintain proper fluid balance. This was perhaps due to a species difference and a sudden increase in weight of this magnitude might produce an increased arterial pressure in an animal with a longer gestation period.

It is of interest to note that the mortality rate among the offspring of the control animals was zero. There was increased mortality in the experimental groups, and the group with the highest mean pressure at delivery showed the greatest mortality rate in their offspring. Thus, there is a positive correlation between arterial pressure and mortality rate regardless of whether the increased pressure is due to DOCA and sodium chloride or to post mineralocorticoid hypertension.

Since blood pressure did not increase during pregnancy in these animals we have failed to simulate the entire clinical picture of preeclampsia. However, we were successful in producing proteinuria and edema and perhaps by selecting a different species the increased arterial pressure might also be produced.

Summary. The influence of pregnancy on arterial pressure, proteinuria, weight, and fetal and neonatal morbidity was studied in 2 groups of animals. Group I, 20 uninephrectomized rats, received DOCA and sodium chloride throughout the entire study. Group II, 10 uninephrectomized rats, was bred after withdrawal of the DOCA sodium chloride regimen. There were marked fluctuations in weight of these animals during the time that they received the DOCA and sodium chloride. Pregnancy did not alter the course of hypertension in either group, but both groups showed increased proteinuria during pregnancy. Only 66% of the offspring of Group I was born alive and only 75% of the offspring of Group II were born alive. During the third week of pregnancy, 6 of the animals in the hypertensive groups experienced more than a 10% increase in weight during a 24-hour period and 3 of them convulsed. These data suggest that the fluid balance is affected when pregnancy is superimposed on this type of experimental hypertension.

1. Page, E. W., Glendening, M. G., Proc. Soc. Exp. Biol. and Med., 1953, v82, 466.

2. Rosas, R., Miyata, T., Hoobler, S. W., Bohr, D. G., ibid., 1963, v113, 456.

3. Langston, J. B., Guyton, A. C., Douglas, B. H., Dorsett, P. E., Cir. Res., 1963, v12, 508.

4. Douglas, B. H., Guyton, A. C., Langston, J. B., Bishop, V. S., Am. J. Physiol., 1964, v207, 669.

5. Masson, G. M. C., Mikasa, A., Yasuda, H., Endocrinology, 1962, v71, 505.

6. Masson, G. M. C., Corcoran, A. C., Page, I. H., A.M.A. Arch Path., 1952, v53, 217.

7. Harrison, T. R., Grollman, A., Williams, J. R., Jr., Am. J. Physiol., 1940, v128, 716.

8. Friedman, M., Freed, S. C., Proc. Soc. Exp. Biol. and Med., 1949, v70, 670.

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