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The role of pregnancy in the induction of the generalized Shwartzman reaction

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The generalized Shwartzman reaction could be produced by a single injection of endotoxin into "pregnant" rats after hysterectomy as well as shortly after spontaneous delivery. If 12 to 24 hours elapsed between delivery and endotoxin injection, the reaction could not be induced any more. The results yield additional evidence for the thesis that pregnancy is accompanied by an increased susceptibility to consumption coagulopathy. Yet, the uterus, placenta, and fetus seem to play only an indirect and possibly minor role in the "preparatory" mechanism by pregnancy.

CONSUMPTION coagulopathy and bilateral renal cortical necrosis as they are typical of the generalized Shwartzman reaction are found in pregnant women in connection with septic abortion.[1, 2] The importance of pregnancy is underlined by the experimental findings that the generalized Shwartzman reaction can be produced in pregnant animals by a single injection of endotoxin.[3, 4] In septic abortions the generalized Shwartzman reaction may be seen already in the first trimester of pregnancy. On the other hand, consumption coagulopathy in relation to pregnancy may still occur after hysterectomy or emptying of the uterus. This raises the question of whether the uterus, fetus, and/or placenta are necessary for the induction of consumption coagulopathy.

In this study, the role of the uterus, fetus, and placenta for the induction of the generalized Shwartzman reaction was investigated in the rat.

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Table I. Incidence of glomerular capillary thrombosis after an intravenous injection of endotoxin into pregnant rats hysterectomized on the twentieth or sixth day of gestation as well as into sham-operated animals

	Hysterectomy	*Sham operation*	*Hysterectomy*
Day of gestation	20	20	6
Incidence of glomerular capillary thrombosis	13/18	5/6	0/6
Percentage of glomerular capillary thrombosis	72	83	0

Material and methods

Pregnant and nonpregnant female albino rats (200 to 300 grams) were intravenously injected with 400 μg of *Escherichia coli* endotoxin O55:B5 (Difco Labs., Detroit, Michigan) dissolved in 1 ml. of sterile, pyrogen-free physiologic saline solution. The endotoxin was injected at different intervals after delivery (see Table II). Hysterectomy (uteri, fetuses, and placentas) was performed on the twentieth day of gestation under ether narcosis and lasted about 15 to 20 minutes. In sham-operated pregnant as well as nonpregnant animals, the uterus was pulled out of the abdominal cavity and reposited, and the abdominal walls were sutured. Endotoxin was injected 15 minutes after finishing the sham operation as well as hysterectomy. The animals were killed 24 hours after the injection of endotoxin if they had not already died; necropsies were performed immediately after death. Histologic sections of the kidneys were examined for fibrin thrombi with hematoxylin and eosin stains and the histochemical technique of Adams.[5]

Results

Tables I and II summarize the results. By a single dose of endotoxin, the generalized Shwartzman reaction could be induced in pregnant as well as in hysterectomized rats which were at the twentieth day of gestation. Control pregnant rats which were hysterectomized and then injected with endotoxin on the sixth day of gestation did not develop the generalized Shwartzman reaction. These controls seemed to be essential to exclude the influence of the operation on the induction of the generalized Shwartzman reaction. Furthermore, sham operation of pregnant rats on the twentieth day of gestation did not affect the occurrence of the generalized Shwartzman reaction.

If rats were allowed to deliver and were injected with endotoxin within the first 45 minutes after delivery, the generalized Shwartzman reaction could be elicited at the same percentage as in the controls (Table II). In the hours following delivery, the incidence of fibrin thrombi in the glomerular capillaries after endotoxin injection decreased to the extent that 12 and 24 hours after delivery the generalized Shwartzman reaction could no longer be produced.

Comment

The mechanism of "preparation" for the generalized Shwartzman reaction is not clear. The present study demonstrates the minor importance of the uterus, fetus, and placenta for the induction of the generalized Shwartzman reaction. In hysterectomized postpartum rats as well as in animals shortly after spontaneous delivery, the reaction could still be elicited. Therefore, placental damage and fetal death have to be interpreted as epiphenomena produced by a direct effect of endotoxin or secondary to disseminated intravascular coagulation. The escape of clot-promoting agents out of the uterus into the general circulation cannot be made responsible for triggering generalized intravascular coagulation after endotoxin injection. This concept had been proposed by Galton[6] to explain the mechanism by which colchicine induced the generalized Shwartzman reaction in the pregnant golden hamster. However, we also succeeded in inducing the generalized Shwartzman reaction by colchicine in hysterectomized postpartum rats.[7]

The most likely explanation of how pregnancy "prepares" for the generalized Shwartzman reaction is the alteration in the hemo-

Table II. Incidence of glomerular capillary thrombosis after an intravenous injection of endotoxin into pregnant rats (controls) as well as into postpartum rats at different intervals after spontaneous delivery

	Controls (Day 20 of gestation)	*Hours after delivery*					
		¾	1½	3	6	12	24
Incidence of glomerular capillary thrombosis	17/22	13/17	8/14	6/16	5/14	0/14	0/17
Percentage of glomerular capillary thrombosis	77	76	57	37	35	0	0

static mechanism during pregnancy. The "hypercoagulable state" during pregnancy might well be related to fibrinogen metabolism with the occurrence of circulating fibrinogen derivatives with a molecular weight higher than the parent molecule.[8] The reduction of the spontaneous fibrinolytic activity, that is, a markedly prolonged euglobulin lysis time before and at delivery, especially seemed to be of considerable significance because the "preparatory" effect of pregnancy can easily be substituted in nonpregnant rats by fibrinolysis inhibition. The generalized Shwartzman reaction could be induced in nonpregnant rats by thrombin[9] as well as by colchicine[7] if the fibrinolytic system was inhibited by epsilon-aminocaproic acid. The normalization of the lytic system after delivery is very rapid and in women already is reached 24 hours after delivery.[10, 11] These findings may explain why in the present study the generalized Shwartzman reaction could be induced before and only up to a few hours after delivery.

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