INTERACTION BETWEEN THE GRAFT VERSUS HOST REACTION AND PREGNANCY

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A graft versus host reaction (GVHR) was induced in F_1(CBA × C57BL/6) female hybrids by intravenous injection of a suspension of lymphocytes from the spleen and lymph glands from C57BL/6 females. Pregnancy, which developed as a result of crossing the experimental females with syngeneic males 1-10, 10-20, 30-40, and over 40 days after injection of the lymphocytes, aggravated the transplantation sickness due to the GVHR. On the other hand, the GVHR under these conditions reduced the percentage of animals that became pregnant and disturbed the reproductive function of the experimental mice (stillbirth, death of the pregnant females, abortion). An exacerbation of the GVHR was observed in some of the experimental animals after giving birth. The rate of survival of the progeny was lowered.

KEY WORDS: graft versus host reaction; pregnancy; survival rate; immunologic connections between mother and fetus.

The graft versus host reaction (GVHR) developing after injection of immunocompetent cells into an immunologicaly unprotected host can lead to the onset of various pathological states [1, 3, 8, 9].

Despite the many investigations devoted to the study of various aspects of the GVHR, the differences in the development of this reaction during pregnancy have still not been studied. Yet the importance of such a study is evident. First, there are reports that maternal lymphocytes can enter the fetus under natural conditions [5, 10] and induce a GVHR and pathological changes in it [4, 6, 7]. Second, a GVHR may arise as a result of artificial manipulations (transplantation of bone marrow and lymphoid tissue) during pregnancy.

The objects of this investigation were, first, to study the effect of pregnancy on the course of the GVHR and, second, to investigate the effect of the GVHR on the course of pregnancy.

EXPERIMENTAL METHOD

Inbred mice were obtained from the Stolbovaya Nursery, Academy of Medical Sciences of the USSR. The GVHR was induced in female F_1(CBA × C57BL/6) hybrids by injecting lymphocytes from the spleen and lymph glands of C57BL/6 females aged 16-18 weeks. The age of the hybrids was 10-12 weeks and their weight 20-22 g. The suspension of lymphocytes was prepared as described previously [2] and injected into the retroorbital venous sinus of the recipients in doses of between 22 and 60 million. In the experiments of series I the female hybrids were crossed with syngeneic males 1 and 10 days, and in series II 30, 40, or more days after the induction of GVHR. The fertilizing ability of the males had been verified beforehand. In series III the GVHR was induced in female hybrids on the 1st-5th day after conception.

Female F_1(CBA × C57BL/6) hybrids of the same age and weight, receiving an equal dose of lymphocytes to the experimental animals but not subsequently mated, and 27 normal hybrid females crossed with syngeneic males were used as the controls.

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TABLE 1. Effect of Pregnancy on Course of GVHR

Series of experiments	Group No.	Time (days) after induction of GVHR to beginning of pregnancy	No. of females mated	No. of animals dying at different times after induction of GVHR			No. of mice dying in 3 months (%)		No. of mice dying in 1 year (%)	
				10—30 days	31—60 days	61—90 days	$M \pm m$	P	$M \pm m$	P
I	1 2	1—10 10—20	75	45	12	—	76,0±4,8	<0,01	82,7±4,4	<0,01
	Control	GVHR without pregnancy	69	28	5		47,8±6,0	—	53,0±6,0	—
II	3 4	30—40 over 40	23	4	3	5	52,2±10,6	<0,01	69,6±9,8	<0,01
	Control	GVHR without pregnancy	24	2	2	—	16,6±7,8	—	16,6±7,8	—

TABLE 2. Effect of GVHR on Pregnancy

Series of experiments	Group No.	Time of onset of pregnancy before or after induction of GVHR	No. of females mated	No. becoming pregnant			Result of pregnancy and parturition						Survival rate of progeny during first month of life (%)	
							birth of living mice			still-birth	death of pregnant mice in 2nd-3rd term	death of mice after abortion		
				abs.	% ($M \pm m$)	P	No. of mice*	% of those pregnant ($M \pm m$)	P				$M \pm m$	P
	1	1-10 days after	42	25	59,7±7,6	<0,02	11/86	44,0±10,1	<0,01	1	7	6	79±4,41	<0,01
	2	10-20 days after	33	18	54,5±12	<0,02	11/81	61,1±11,8	<0,05	3	2	2	74,0±4,5	<0,01
	3	30-40 days after	9	8	88,8±11,1	>0,05	5/43	62,5±18,3	<0,05	—	—	3	55,8±7,6	<0,01
II	4	More than 40 days after	10	10	100±31,1	>0,05	10/57	100±33,1	>0,05	—	—	—	44,2±6,2	<0,01
III	5	1-5 days before	13	13	100±23,5	>0,05	0	0±23,5	<0,01	—	10	3	—	—
Control		Pregnancy without GVHR	27	27	100±13,0	—	27/170	100±13,0	—	—	—	—	93±3,4	—

* Number of mice giving birth to living young shown in numerator, number of young in denominator.

EXPERIMENTAL RESULTS

In the experiments of series I 75 experimental and 69 control animals were used, and in series II 23 experimental and 24 control animals. The effect of pregnancy on the GVHR was assessed from the mortality of the experimental and control mice over a period of 3 months and 1 year (Table 1). The percentage of dying experimental mice in the two series was clearly significantly higher than in the control.

The effect of GVHR on pregnancy is reflected in Table 2. Injection of lymphocytes of F_1 hybrid females 1-10 and 10-20 days before the beginning of pregnancy significantly reduced the percentage of mice becoming pregnant. In these cases pregnancy perhaps did not develop because of disturbance of the implantation stage. The frequency with which the females in the experiments of series I gave birth to living young also was significantly lowered.

In the experiments of series II, in the group in which pregnancy began 30-40 days after induction of the GVHR, the percentage of females becoming pregnant was close to 100, but the frequency of births was reduced. In the group in which the hybrids were mated 40 days after induction of the GVHR, all 10 experimental mice became pregnant and gave birth to living progeny.

Exacerbation of the GVHR was observed in some of the experimental animals in both series at different times after parturition and was accompanied by severe dermatitis and diarrhea. The exacerbation was particularly marked in animals in series II, where five of these mice died between 11 and 53 days after parturition. Histological examination of the lymphoid organs of these animals revealed extensive areas of sclerosis in the spleen (the weight of the spleen reached 34 mg) and atrophic changes in the thymus and lymph glands.

The mean number of young mice in the litter in the experimental series was only slightly different from that in the control. However, the newly born young of the F_1 mothers which received lymphocytes before pregnancy were weak and malnourished in some cases. Their mortality was high in the first month of life (Table 2).

Observations on the experimental mice surviving from both series of experiments and the surviving animals after induction of GVHR (GVHR without pregnancy) continued for 1 year. The animals were smaller in weight (27.0 ± 0.6 g in series I, 29.0 ± 0.4 g in series II, 28.8 ± 0.4 g in the group of GVHR without pregnancy, compared with 39.0 ± 0.8 g in the group of pregnant animals without GVHR; $P < 0.01$). The animals were killed 1 year after induction of the GVHR and the weight of the lymphoid organs (spleen 187 ± 31 mg in series I, 165 ± 29 mg in series II, 129 ± 10 mg in the GVHR without pregnancy group compared with 87 ± 2.0 mg in the pregnancy without GVHR group; $P < 0.01$; thymus 16 ± 1.5 mg in series I, 27 ± 2.2 mg in series II, 21 ± 2.1 mg in the GVHR without pregnancy group compared with 37 ± 0.7 mg in the pregnancy without GVHR group; $P < 0.01$) and the results of inspection showed the development of a chronic GVHR in the surviving animals.

In the experiments of series III (induction of GVHR in the early stage of pregnancy) intrauterine death of the fetuses at different stages of development was observed in 10 of the 13 pregnant mice.

The results thus demonstrate an effect of pregnancy on the course of the GVHR in F_1 hybrid females, manifested as a decrease in the life span of the experimental animals and exacerbation of the GVHR after parturition.

Injection of parental lymphocytes from the C57BL/6 females into F_1(CBA $\times$ C57BL/6) hybrid females, followed by mating the hybrids with syngeneic males, on the other hand, led to a reduction in the percentage of animals becoming pregnant and to a disturbance of the reproductive function of the females (stillbirth, death of the pregnant females, abortions, death of the newborn mice). Injection of parental lymphocytes to the F_1 hybrid females on the 1st-5th day after conception was followed by intrauterine death of the fetuses at different stages of development.

The results indicate the need for extreme caution when answering the question of the desirability of transplantation of lymphoid and hematopoietic tissue before or during pregnancy. This could lead to complications affecting both the mother and the fetus.

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