EFFECT OF FEVER IN EARLY PREGNANCY ON CIRCULATION IN THE UTERUS AND PLACENTA OF RABBITS

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The harmful effect of fever in early pregnancy on the fetus was shown in a previous investigation. Disturbance of the placental circulation is of great importance in the mechanism of these harmful effects. These disturbances take the form of inadequate vascularization of the fetal placenta, irregular distribution of the fetal vessels in the placenta, and disturbances of transformation of the cytotrophoblast into the plasmoditrophoblast [1, 2].

The object of the present investigation was to examine quantitatively the vascularization of the placenta in these conditions.

EXPERIMENTAL METHOD

Of the existing methods [3-6], the simplest from the technical point of view is that of measuring the area of tissue on histological preparations by means of the ocular micrometer grid proposed by Eränko [6]. This method was used by A. A. Cheremnykh [4] to study the area of the capillary bed in human and animal fetuses and neonates.

The vascular bed of the placenta was investigated quantitatively on the 12th and 15th days of pregnancy. At these times the fetal blood still contained many nucleated erythrocytes (erthroblasts) and is easily distinguished from maternal blood. Experimental fever was produced in the rabbits at the following times of pregnancy: 4th day (before implantation) and 10th day (beginning of placentation). The control group consisted of pregnant rabbits not subjected to harmful influences. A febrile reaction was evoked in the animals by two subcutaneous injections of a killed culture of Bacillus mesentericus with a titer of 1.5-2 billion bacterial cells/ml. On the 12th and 15th days of pregnancy, laparotomy was performed on the rabbits under local procaine anesthesia. The fetuses were extracted from the uterine cornu through an incision in the antimesometrial side and studied by means of a dissecting microscope. For histological examination of the placentas they were embedded in paraffin wax and sections cut to a thickness of 8 μ were stained with Carazzi's hematoxylin and eosin and with azure II-eosin.

The ocular micrometer grid used was a square measuring 0.5 cm along its side and divided into 100 small squares. The section passed through both lobes of the placenta in their largest cross section. In each placenta 20 fields of vision were investigated: 10 in the superficial and 10 in the deep part. The number of squares of the grid occupied by fetal vessels and by maternal blood were counted under the microscope with a magnification of 1:400, and the mean area of the maternal and fetal vascular beds was calculated (as percentages for each group of animals).

EXPERIMENTAL RESULTS

Experiments were carried out on 67 pregnant rabbits; 26 pregnant animals were used as controls. Altogether 748 placentas were studied.

As the figure shows, the fetal vessels on the 12th day of pregnancy (after fever on the 4th day) occupied one-quarter of the area in the superficial portions of the placenta ($P < 0.01$) and one-eighth in the deep portions ($P < 0.01$) compared with the controls. Almost the same differences, but to a lesser degree, were observed after fever on the 10th day of pregnancy.

A marked increase in the area of fetal vessels was observed between the 12th and 15th days of pregnancy after fever on the 10th day (two-fold increase; $P < 0.01$) and especially after fever on the 4th day of

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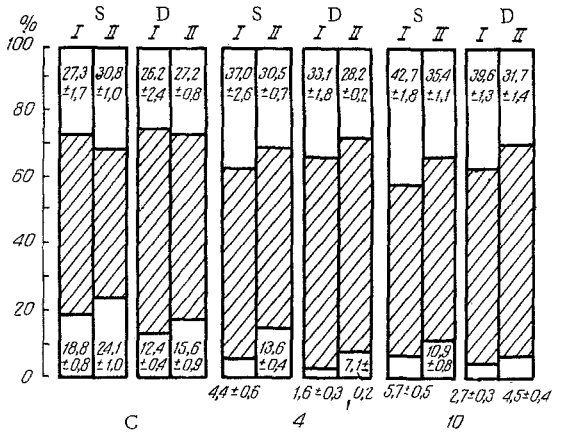

Distribution of area (in percent) occupied in superficial (S) and deep (D) portions of the placenta by maternal (above) and fetal (below) vascular beds and by other tissues (mesenchyme, trophoblast; shaded part of column) on 12th (I) and 15th (II) days of pregnancy in control (C) and after fever on the 4th (4) and 10th (10) days of pregnancy.

pregnancy (by three times in the superficial portions, $P < 0.01$; by 4.5 times in the deep portions of the placenta, $P < 0.01$). By comparison with the controls, however, the area of the fetal vascular bed in both groups was still less than half ($P < 0.001$).

The increase in area of the fetal vessels in the placenta by the 15th day of pregnancy was accompanied by a decrease in hyperemia of the trophoblastic sinuses. The area occupied in the placenta by maternal blood after fever on the 4th day of pregnancy was almost indistinguishable from the area of the maternal vascular bed of the placenta in the control observations, while after fever on the 10th day of pregnancy it exceeded the control area even more ($P < 0.01$).

Additional investigations after fever on the 8th day of pregnancy (period of implantation) revealed that besides hemorrhages in the placenta observed on the 12th day of pregnancy, the area of the maternal vascular bed was almost indistinguishable from that in the control, while the decrease in area of the fetal vessels in the superficial (13.8 ±0.4% compared with 18.8 ± 0.8% in the control; $P < 0.01$) and deep (6.9 ± 0.3% compared with 12.4 ± 0.4% in the control; $P < 0.01$) portions showed no harmful action on the fetus and the mortality among the fetuses of the experimental animals was not higher than that of the control rabbits. Consequently, congestive hyperemia of the uterus is the unfavorable factor determining the disturbance of fetal development; it may reduce the area of the fetal vascular bed, as was seen after fever on the 10th day of pregnancy: the hyperemic trophoblastic sinuses compressed the fetal vessels.

A sharp increase in area of the fetal vessels between the 12th and 15th days of pregnancy, after fever on the 4th and 10th days, is evidence of repair processes.

The improvement in the placental circulation between the 12th and 15th days of pregnancy after fever on the 4th day also had a favorable effect on intrauterine development of the fetuses, as the author has shown previously [2]; the proportion of fetuses with retarded development was halved (from 38.6 ± 5.8% on the 12th day to 19.1 ± 4.9% on the 15th day of pregnancy; $P < 0.01$), and the mortality among the fetuses increased slightly (from 17.1 ± 4.43% to 23.8 ± 5.39%; $P > 0.05$).

The results were different after fever on the 10th day of pregnancy. Despite an increase in area of the fetal vessels between the 12th and 15th days, vascularization of the deeper portions of the placenta was deficient: although the area of the fetal vessels in these portions had increased by 1.6 times ($P < 0.01$), it was still 3.5 times less ($P < 0.01$) than in the control. Congestive hyperemia of the trophoblastic sinuses was also observed in these cases. The conditions of development of the fetuses were accordingly impaired, and their mortality by the 15th day of pregnancy increased from 9.5 ± 2.19 (on the 12th day) to 26.2 ± 5.43% ($P < 0.01$).

Later, however, as the author's previous investigations [1, 2] showed, between the 15th and 20th days of pregnancy the state of the fetuses deteriorated sharply after fever on the 4th day (the proportion of dead and developmentally retarded fetuses increased), while it was almost unchanged after fever on the 10th day of pregnancy. This was evidently due to ability of the fetuses to adapt themselves to some of their conditions of development, as was confirmed by the effects of fever on the 8th day of pregnancy: despite the severe disturbances of the placental circulation, the fetuses not only survived, but showed no developmental abnormalities.

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