

# PENICILLIN PERMEABILITY OF THE PLACENTAL BARRIER AT VARIOUS STAGES OF PREGNANCY

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Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 50, No. 12,

pp. 90-93, December, 1960

Original article submitted September 29, 1959

Despite some progress made in the field of study of the fundamental properties of the placenta, many problems concerned with the functions of this organ have so far received inadequate attention. A problem worthy of study is the passage of drugs, introduced into the mother for prophylactic or therapeutic purposes, through the placenta.

Many authors have demonstrated the passage of drugs through the placenta in animals and man: streptocide [4], labeled caffeine [5], antipyrin [1], streptomycin [3, 11, 12], erythromycin [9], vitamins [6, 10] and so on.

In order to discover the action of drugs on the development of the intrauterine fetus, however, it is important to determine the degree of permeability of the placental barrier at various stages of pregnancy. The study of the permeability of the placenta to drugs is of great interest in connection with the real risk of intrauterine involvement of the fetus in certain diseases of the mother.

Antibiotics are used at the present time for the prevention and treatment of many diseases in pregnant women. Penicillin is widely used for these purposes. Several workers have concerned themselves with the study of the permeability of the placenta to this particular antibiotic [2, 7, 8]. They have investigated the penicillin permeability of the placenta during labor or immediately before.

The extension of our knowledge of the degree of permeability of the placenta to penicillin, administered to the mother at various stages of pregnancy, would be of help in the study of problems concerned with the antenatal care of the fetus.

Our object was to make an experimental study of the permeability of the placenta to penicillin at the principal stages of embryonic development.

## METHOD

For the experiments we used primiparous white rats, bearing in mind that this species of laboratory animal is often chosen for experimental research. Moreover, the placenta of this species of animal, like the human placenta, has a hemochorial type of structure. To obtain pregnant animals, females were caged with males for 24 hours (in a ratio of one male to 5-6 females). The rat was considered to be pregnant from the moment that spermatozoa were found in the vaginal smear. The initial body weight of the rats on the first day of pregnancy was 170-200 g.

Penicillin Concentration in the Blood of Pregnant Rats and Fetal Tissues after Injection of the Antibiotic at Various Stages of Pregnancy (in units/ml)

Day of pregnancy	Material investigated	Time after injection of penicillin					
		30 min		2 hr		3 hr	
		no. of ani- mals	concentration of penicillin	no. of ani- mals	concentration of penicillin	no. of ani- mals	concentration of penicillin
11th	Blood of pregnant rats	8	61.44-15.36 (mean 23.0)	6	0.96-0.24 (mean 0.48)	7	0.48-0.12 (mean 0.26)
	Fetal tissues	8	0.24-0.03 (mean 0.08)	6	0.12-0.03 (mean 0.07)	7	0.12-0.03 (mean 0.06)
16th	Blood of pregnant rats	6	30.72-15.36 (mean 27.7)	7	0.96-0.24 (mean 0.4)	7	0.24
	Fetal tissues	6	0.12-0.03 (mean 0.06)	7	0.12-0.03 (mean 0.07)	7	0.12-0.03 (mean 0.06)
20th	Blood of pregnant rats	10	30.72-15.36 (mean 26.9)	5	0.48-0.24 (mean 0.33)	6	0.24-0.06 (mean 0.23)
	Fetal tissues	10	0.96-0.48 (mean 0.67)	5	0.96-0.24 (mean 0.64)	6	0.96-0.24 (mean 0.62)

The permeability of the placenta was investigated on the 11th, 16th, and 20th days of pregnancy, and correlated with the developmental and structural features of the placenta in rats at these times.

Penicillin was injected in a dose of 20,000 units/kg body weight. The calcium salt of penicillin was injected intramuscularly into the right hindlimb.

The permeability of the placental barrier was studied by the comparative analysis of the penicillin content of the maternal and fetal tissues by means of the serial dilution micromethod of Z. V. Ermol'eva and E. A. Ved'mina [3]. This method is sufficiently sensitive and can be used to determine the penicillin concentration in the blood with an accuracy of 0.03 units/ml of serum. The test organism was No. 209 Oxford strain of *Staphylococcus aureus*, and the indicator of growth of the microorganisms was Andrade's reagent. All the experimental animals studied were kept in identical conditions, favoring a normal course of pregnancy.

The experimental rats were divided into three groups corresponding to the days of pregnancy. The animals of the first group (21 rats) received penicillin injections on the 11th day of pregnancy, those of the second group (20 rats) on the 16th day, and those of the third group (21 rats) on the 20th day of pregnancy.

We know from the literature [2] that the penicillin concentration after intramuscular injection reaches a maximum 30 min after injection of the drug, stays at a high level for one hour, gradually falls to the second hour and has almost completely disappeared three hours after injection. Taking these findings as a guide we investigated the penicillin concentration in the blood of the rats and in the tissue juices of the fetuses 30 min and 2 and 3 hr after the drug was injected into the pregnant animals. Blood was obtained from the carotid arteries of the pregnant animals by decapitation. Next, with strict observance of the rules of asepsis, the abdomen was opened and the uterus with the contained fetuses extracted. From 5 to 12 fetuses were taken for investigation, depending on the stage of pregnancy. The fetuses (in the early stages of pregnancy, embryos) were freed from their bed in the uterus, separated from the membranes, dried with filter paper, weighed and ground in a mortar by means of a quartz pestle, after which they were treated with a phosphate buffer (pH 7.2-7.4). The mixture thus obtained was centrifuged and the penicillin concentration in the centrifugate was determined. The penicillin concentrations in the blood of the pregnant rat and in the fetal tissues were expressed in units/ml of the biological fluid tested. The results obtained are shown in the table.

## RESULTS

After intramuscular injection of the same dose of penicillin (5000 units) into the animals on the 11th, 16th, and 20th days of pregnancy, variations in the concentration of the antibiotic between different limits were observed. For instance, when determined 30 minutes after injection, the penicillin concentration varied between 61.44 and 15.36 units/ml, falling sharply in the second hour of the investigation to 0.96-0.24 units/ml. After 3 hr the concentration was 0.48-0.12 units/ml. In view of the regularity of the pattern of fall of the penicillin concentration in the blood of the pregnant rats, it may be postulated that to maintain the blood concentration of the antibiotic in pregnant animals, it should be administered at intervals of 3 hours.

A different pattern was observed when the penicillin concentration in the tissues of the embryo was investigated.

Thirty minutes after the intramuscular injection of penicillin into the animals of the second group (11th day of pregnancy), the concentration of the antibiotic in the tissues of the embryos averaged 0.07 units/ml, and remained at approximately this level for 2 and 3 hr.

After the intramuscular injection of penicillin to animals on the 16th day of pregnancy, the concentration of the antibiotic in the fetal tissues was roughly the same as in the embryos of the first group of animals (11th day of pregnancy); when investigated after 30 min it was 0.08 units/ml, and it remained at this level after 2 and 3 hr.

It was thus shown that penicillin can penetrate into the tissues of the embryo even in the early stages of embryogenesis (11th and 16th days), but that its concentration in the embryo was far less than in the maternal blood. The penicillin concentration in the tissues of the embryo was maintained at a constant level longer than in the maternal blood. This is evidently due to the more rapid excretion of penicillin from the mother.

After injection of penicillin into animals on the 20th day of pregnancy it was found that its concentration in the fetal tissues varied between 0.67 and 0.62 units/ml when tested after 30 min. During the next 2-3 hr after injection of the antibiotic, its concentration remained essentially unchanged (0.67-0.62 units/ml).

## SUMMARY

Permeability of the placental barrier to penicillin was studied on pregnant rats on the 11th, 16th, and 20th days of pregnancy. The penicillin concentration was compared in the mother's blood and the fetal tissue fluids at various stages of pregnancy 30 min, 2 and 3 hr after its intramuscular administration in a dose of 20,000 units/kg body weight. The penicillin concentration was examined by Ermol'eva and Ved'mina's serial dilution micro-method. The placenta of white rats is permeable to penicillin on the 11th, 16th, and 20th days of pregnancy; it is more permeable on the 20th day than on the 11th and 16th days. The concentration of antibiotic in the mother's blood is higher than in the fetal tissues. A reduction of the blood penicillin level occurs in pregnant rats much more rapidly than in the fetus.

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