PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

A New Method of Stimulating Uteroplacental Blood Flow, Based on the Regulation of Venous Circulation in the Uterus

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Experiments on pregnant rabbits infused with troxevasin showed that the rate of uteroplacental blood flow after infusion depended on the dose and the initial (preinfusion) rate of this blood flow. After the dose of 140 mg/kg, the blood flow rate increased if it was initially low and decreased if it was high. After a lower dose (70 mg/kg), the blood flow rate decreased to different degrees depending on the initial blood flow rate in the uterus. The findings suggest that the use of troxevasin to treat the fetus is indicated in cases of placental insufficiency.

Key Words: *uteroplacental blood flow; rabbit fetuses; fetal growth retardation; troxevasin*

In recent years infusion therapies have come into wide use in obstetric practice, notably in the combined treatment of late gestational toxicoses (toxemias of pregnancy). Such therapies employ substances with different mechanisms of action, including systemic vasodilators (e.g., euphylline and theophylline), substances altering physical properties of the maternal blood and improving the systemic hemodynamics (low-molecular dextrans), and drugs that selectively stimulate uteroplacental blood flow (e.g., sygethin) or influence the microcirculation and metabolic processes in organs and tissues by modifying rheological properties of the blood and causing vasodilatation (e.g., pentoxifylline).

The substances just mentioned, which are used in obstetrics to correct disordered uteroplacental circulation, mainly stimulate the arterial blood supply to the uterus. However, the reaction to stress begins with venular contraction [8], and impaired venous drainage plays a large role in the genesis of various pathological conditions. Venous pressure may be considerably elevated in women suffering from late gestational toxicosis [2,4,5], while venous pressure elevation in patients with acquired combined organic heart lesions (vitia cordis) is always associated with the emergence of cardiac decompensation which precedes the onset of clinically manifest cardiac insufficiency. A venous pressure change in general and in pregnant women in particular is a very sensitive indicator of circulatory disturbances and an important guide in the diagnosis and prevention of abnormal pregnancies. The usefulness of measures that can improve venous circulation in women with complicated pregnancy is obvious.

One of the drugs that influence venous circulation by improving capillary and venular permeability is troxevasin. To date, however, there have been no reports of its use in obstetric practice for improving uterine blood flow. The present study

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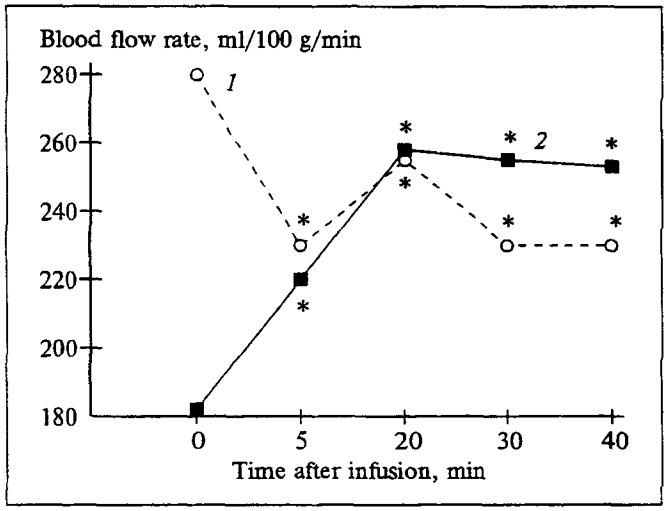

Fig. 1. Variations in uterine blood flow rates after troxevasin infusion at 140 mg/kg. *1*) intact (control) uterine horns with high initial blood flow rate; *2*) uterine horns with low initial blood flow rate (this plot was constructed using averaged data for intact and test horns). Here and in Fig. 2: the asterisk denotes a significant change relative to the initial value.

was undertaken to assess experimentally the potential of a new method of regulating the uteroplacental circulation by modifying venous drainage from the uterus by means of troxevasin infusions.

MATERIALS AND METHODS

The study was carried out on 24 female Chinchilla rabbits (body weight 3-4 kg) and their 44 fetuses. In each female, placental insufficiency was produced on day 18 of gestation by ligating approximately one-third of the preplacental vessels at every other fetal receptacle in one uterine horn. The fetuses of the second uterine horn, in which the circulation remained intact, served as controls. On day 29 of gestation, relaparotomy was performed under intravenous anesthesia with thiopental sodium (1 ml of 5% solution per kg body weight) to implant silver electrodes into the fetuses of the test and control horns for unipolar recording of electrocardiograms. During this operation slender plastic catheters were inserted into the carotid artery and jugular vein of each female to record blood pressure. The catheters were filled with heparin and their outer ends were sealed. The wires from the electrodes and the catheters were passed under the animal's skin and brought to the outside between the ears. In addition, collecting veins were surgically mobilized in both uterine horns and measuring sensors of platinum wire enclosed in a plastic cuff were applied to the veins for measuring the volume rate of uterine blood flow. Hydrogen clearance curves were recorded polarographically [3]. For saturation of the uterus with hydrogen, the females inhaled a hydrogen-rich gaseous mixture for 1 min. Maternal and fetal electrocardiograms were recorded with a Bioscript electroencephalograph, concurrently with measurements of maternal arterial and venous pressures using pressure gauges. As pressure sensors, semiconductor pressure transducers were used, based on tensoresistors (PDP-21000 MD and PDP-400) developed at the All-Union Institute of Medical Instrumentation.

The females were divided into two groups, one of which (n=10) received troxevasin intravenously at 140 mg/kg and the other (n=14) at 70 mg/kg.

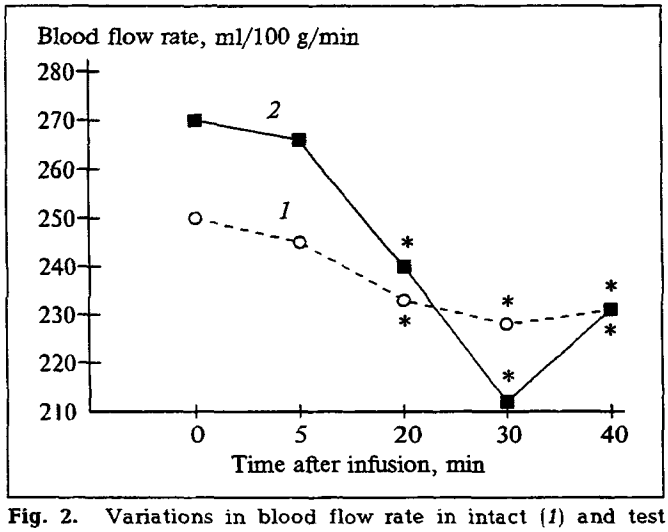

Fig. 2. Variations in blood flow rate in intact (*1*) and test (*2*) uterine horns after troxevasin infusion at 70 mg/kg.

RESULTS

The current technology permits simultaneous recording of maternal and fetal functions in nonanesthetized female rabbits that each carry both test and control fetuses while remaining in a normal state.

After the troxevasin infusion, the uteroplacental blood flow rate changed to different degrees depending on the dose and the initial (preinfusion) flow rate. Thus, after the larger dose (140 mg/kg) the rate increased if it was initially low and decreased if it was high. Regardless of its initial value, the flow rate began to change significantly at 5 min postinfusion, and the greatest increase (40.8±10.1% above the initial level) was recorded at 20 min; the greatest decrease was less marked (24.2±6.3% above the initial level) (Fig. 1).

After the lower troxevasin dose (70 mg/kg), blood flow rates decreased in both the control and test uterine horns (Fig. 2). In these tests the initial blood flow rates were higher than in those using the 140 mg/kg dose. The degree of decrease depended on the initial rate; for example, the test horn in which the initial blood flow rate was 7.3%

lower than in the control horn showed a less marked decrease than the latter. For both the test and control horns, the greatest decreases (by 21.1±4.2% and 8.1±2.3%, respectively) were recorded 30 min after the discontinuation of infusion.

Neither troxevasin dose caused a significant change in maternal venous pressure. Maternal arterial pressure progressively fell in the first 15 min postinfusion and significantly differed (by 8.1±1.2%) from the initial level during 60 min.

The mean heart rate did not change significantly either in the females or in their fetuses. The differences in the response of fetal hearts to infusion of the mother with troxevasin were confined to those in cardiac rhythm fluctuations. In the group given troxevasin at 140 mg/kg, the mean fetal weight in the test horns was on average 8% higher than that in the control horns, but this difference was insignificant, i.e., retardation of fetal growth did not occur despite the ligation of preplacental vessels. The lower fetal weight in the intact horns can probably be accounted for by the natural delay of fetal development in these horns as they contained more fetuses than the test horns.

Fetuses of lower weight, including those from the intact horns, showed decreased cardiac rhythm fluctuations after troxevasin infusion, whereas the reverse was true of fetuses of higher weight from the test horns, i.e., these fetuses exhibited the same adaptive reaction to hemodynamic changes in the maternal-placental-fetal system as did their normal counterparts from the control horns.

The findings presented above suggest that substances stimulating uteroplacental blood flow should not be prescribed in the absence of an appropriate indication for their use, namely a reasonably high probability of lowering the intensity of uteroplacental blood flow.

The results of this study are quite amenable to explanation on the basis of findings reported by other authors. Thus, as found by Greiss [8], feeding vessels of the uterus are widened almost to the limit during normal pregnancy so that their response to vasodilators can only be minimal. This may explain why the increase in uteroplacental circulation in response to a vasoactive agent is larger when this circulation is insufficient than when it is adequate. Moreover, the uteroplacental vascular network has been shown to be greatly expanded and to function at peak hemodynamic efficiency during pregnancy. It follows, then, that no further increase in the width of arterial vessels is possible in response to vasodilators and adaptive vasoconstriction occurs instead.

According to Moll and Kunzell [9], no drugs can increase placental blood flow during physiological (normal) pregnancy. This view is consonant with the results of our experimental and clinical study where infusions of rheopolyglucin and trental (pentoxifylline) were shown to improve hemodynamic parameters in a functional maternal-placental-fetal system if their initial values deviated from normal - both in animals with artificially induced placental insufficiency and in women with severe forms of late gestational toxicosis involving a lowered volume rate of uteroplacental blood flow. Furthermore, findings in our laboratory and those reported in the literature indicate that, regardless of how the drugs used to improve uteroplacental circulation act, the changes they cause in the rate of uterine blood flow consistently depend on its initial rate, so that the rate is increased if it is initially low and decreased if it is high.

The findings from the present experimental study show that the use of troxevasin to treat the fetus is indicated when there is evidence of placental insufficiency. There are sufficient grounds for initiating clinical trials on women with placental insufficiency and retarded fetal growth.

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