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Effects of Prostaglandins and Inhibitors of Prostaglandin Synthesis in the Fetus and Newborn Infant

Fetal tissues, including the placenta, have been shown to contain significant amounts of prostaglandins (PG) and also to have the capacity to synthesize PG. Furthermore, PGE_2 and F_2 have been demonstrated in fetal blood, but circulating levels drop rapidly after birth. PGE_1 infusion into fetal lambs produced a marked increase in blood flow to the lungs, myocardium, adrenal gland, and musculo-skeletal system. However, the studies do not indicate the role of PGs in normal regulation of circulatory function in the fetal lamb in utero. Administration of drugs that inhibit synthesis of PGs provides the opportunity to assess their role.

Inhibition of PG synthesis in fetal lambs in utero produced a small increase in combined ventricular output, and in umbilical-placental blood flow, a marked increase in myocardial and adrenal flows, and a small rise in pulmonary flow. Blood flow to the peripheral and gastrointestinal circulations were reduced. PGs thus do not have a significant role in regulating blood flow to the placenta or the lungs in the normal fetus but may exert a mild peripheral vasodilator effect.

Evidence is increasing that PGs have an important role in maintaining dilatation of the ductus arteriosus during fetal life. PGE_1 and PGE_2 produced striking relaxation of isolated strips of ductus arteriosus obtained from fetal lambs. We found that acetylsalicylic acid, indomethacin, or naproxen resulted in constriction of the ductus, with a rise in pulmonary arterial pressure in fetal lambs in utero (2). It is not known whether the ductus is influenced by locally-produced PGs alone or also by circulating PGs. The ductus arteriosus produces PGE_2 and $PGF_{2\alpha}$ in small amounts, but the main PG found was 6-keto-$PGF_{1\alpha}$, a metabolic product of the more active precursor, prostacyclin or PGI_2. However, PGE_2 has a much greater dilator action on the lamb ductus arteriosus than does PGI_2, on a molar concentration basis (1). The relative roles of oxygen and of removal of the PG relaxation effect, in constriction of the ductus arteriosus after birth, have not been resolved. Since circulating PG levels fall rapidly after birth, removal of their effect on the ductus may be important in postnatal ductus closure.

The dilator effect of PGE_1 and E_2 on the ductus arteriosus has been used to treat infants with congenital heart disease in whom the ductus is important in maintaining pulmonary or systemic blood flow. In infants with lesions that obstruct right ventricular outflow, pulmonary blood flow after birth is dependent on flow from the aorta through the ductus arteriosus. In infants with pulmonary atresia, while the ductus is open, pulmonary flow is adequate and there is mild hypoxia. Constriction of the ductus decreases pulmonary flow and results in severe hypoxia. PGE_1 has been infused at rates of 0.05 - 0.1 micrograms/kg per minute in these infants with dramatic improvement in PO_2 (3). Infants with interruption of the aortic arch are dependent on the ductus arteriosus to provide blood flow from the pulmonary artery to the descending aorta. When the ductus constricts, blood flow and arterial pressure in the descending aorta decrease. Infusion of PGE_1 may result in a marked increase in descending aortic pressure and decrease of the pressure gradient across the ductus arteriosus in these infants.

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There is a high incidence of persistent patency of the ductus arteriosus in premature infants, especially those under 1500g in weight. The patent ductus frequently results in cardiorespiratory failure, which may not respond to treatment with digitalis and diuretic drugs and many premature infants have required surgical ligation of the ductus. Since indomethacin constricted the ductus arteriosus in fetal rodents and lambs, we tested the potential of the drug to close the ductus in premature infants with cardiorespiratory failure unresponsive to digitalis and diuretics (4). Indomethacin is given either by orogastric tube, as a suspension, or, if available, intravenously as the lyophilized preparation in a dose of 0.2 mg/kg body weight. If there is an excellent response, no further therapy is indicated. If there is no response or only a partial response, a second and, if necessary, a third dose is given after 8-12 hours intervals. If no response occurs, no further indomethacin therapy is advised, in view of the risk of complications. The most important complication is oliguria, which may progress to anuria. In our experience with the first 100 infants, 70 showed good clinical response and did not require further therapy; 10 showed good initial response but symptoms returned within a week and they required a second course of therapy with good maintained improvement; 5 infants responded partially and still needed digitalis and diuretic therapy; 15 babies showed inadequate or no response and required surgical ligation. In view of the effectiveness of indomethacin, we no longer use digitalis drugs in initial treatment of cardiorespiratory failure in premature infants with patent ductus arteriosus, but administer indomethacin. Current contraindications to its use include necrotizing enterocolitis, bleeding tendencies, and serum creatinine level above 1.6 mg/dl.

Since PG synthesis inhibitors readily cross the placenta, they have the capability of constricting the ductus arteriosus in the fetus when administered to the mother; constriction of the ductus results in an increase in pulmonary arterial pressure. In studies in fetal lambs we demonstrated that a prolonged rise in pulmonary arterial pressure stimulates the growth of the smooth muscle in the precapillary arterioles of the lung (5). The possibility that this increased pulmonary vascular medial muscle development may be responsible for the clinical syndrome of persistent pulmonary hypertension, or persistent fetal circulation in the newborn infant, has been considered. There is already evidence to indicate that persistent pulmonary hypertension occurs in human infants when mothers have ingested aspirin or indomethacin. The condition results from an inability for the pulmonary circulation to undergo the usual dilatation after birth, so that pulmonary vascular resistance remains high and there is thus an inadequate pulmonary blood flow with right-to-left shunting through the foramen ovale with marked cyanosis.

We are not sure how frequently prostaglandin synthesis inhibitors results in this syndrome in human infants. Factors that may influence the effects on the pulmonary circulation are the duration of therapy, dose administered, and period of gestation when ingested. However, until these factors are determined, caution should be exercised in administering drugs which inhibit prostaglandin synthesis to pregnant women.

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