Drug Therapy in Autoimmune Diseases

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This article will review the therapeutic implications for the three groups of drugs most commonly employed in treating pregnant patients with autoimmune diseases—salicylates, corticosteroids, and immunosuppressants. Each section will focus on the perinatal risks associated with the use of these agents.

Salicylates

Salicylates are not only among the medications commonly employed in the treatment of autoimmune diseases but are also consumed by many pregnant patients. Over 200 products, the majority of which are available over the counter, contain acetylsalicylic acid or sodium salicylate. The Collaborative Perinatal Project estimated that approximately 30% of pregnant women used these agents during the first trimester, while 64% of all pregnant patients consumed salicylates at some time during their pregnancy.[1]

Salicylates have important effects on hemostasis. These drugs block platelet cyclooxygenase, an enzyme essential for the synthesis of thromboxane and prostacyclin, which mediate platelet aggregation.[2] After aspirin exposure, cyclooxygenase is irreversibly acetylated for the 10-day life span of the platelet. When platelet malondialdehyde levels have been determined, they can be used in the estimation of the interval since the ingestion of salicylates.[2]

After the administration of as little as 50–100 mg of aspirin, platelet function may be impaired for 5–10 days. Studies of neonates delivered after maternal ingestion of aspirin have demonstrated decreased platelet aggregation, with inhibition of collagen-induced platelet aggregation and suppression of factor XII activity.[3] Stuart and her colleagues have recently assessed the impact of salicylate ingestion on both maternal and neonatal outcome.[2] Prior aspirin ingestion was documented by decreased platelet levels of malondialdehyde. These authors noted hemostatic abnormalities in only 1 of 34 maternal-neonatal pairs in which there was no history of aspirin ingestion. However, in 6 of 10 mothers and 9 of 10 infants in which maternal ingestion of aspirin had occurred within 5 days of delivery, impaired hemostasis could be demonstrated. The mothers exhibited increased intrapartum or postpartum blood loss. Neonatal hemostatic abnor-

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Clinical Obstetrics and Gynecology, Vol. 26, No. 3, September 1983

malities included numerous petechiae over the presenting part, hematuria, cephalohematoma, subconjunctival hemorrhage, and bleeding from a circumcision. Among seven mothers who ingested aspirin in the immediate postpartum period, four demonstrated impaired hemostasis. The authors concluded that the use of aspirin is best avoided during pregnancy and at delivery. However, if ingestion has occurred within 5 days of delivery, they emphasize that the neonate should be carefully examined for the presence of clinical bleeding.

Intracranial hemorrhage in the premature infant has become an increased concern. Rumack and her associates have recently linked maternal aspirin ingestion with an increasing incidence of intracranial hemorrhage in pregnancies complicated by premature delivery.[4] The authors used historic data in order to determine those mothers who had taken 1 or more aspirin tablets within 1 week of delivery and compared neonatal outcomes with mothers who had not taken aspirin. The presence of intracranial hemorrhage was documented by computed tomographic scanning. In a control population of 71 patients, intracranial hemorrhage occurred in 44% of infants delivered at or before 34 weeks and in 49% of infants weighing 1500 g or less. These figures were significantly higher in premature infants who had been exposed to aspirin in utero. The incidence of intracranial hemorrhage rose to 71% for infants at 34 weeks' gestation or less and to 83% for premature infants weighing 1500 g or less. It is possible that aspirin not only increased the incidence of these hemorrhages but worsened their severity. The authors failed to provide important perinatal information in this study, such as the method of delivery or the presence of intrapartum asphyxia. They concluded, however, that the advisability of aspirin use during the final 3 months of pregnancy was highly questionable.

The ability of salicylates to block the cyclooxygenase enzyme and thus prevent the synthesis of all prostaglandins has important consequences on fetal circulatory function.[5] In fetal life, blood normally passes from the right ventricle into the main pulmonary artery, to the ductus arteriosus, and then to the descending aorta. Almost 90% of right ventricular blood is directed through the ductus, whereas only 10% enters the pulmonary circulation. Normally, the pressures in the pulmonary artery and aorta are almost identical. Studies in fetal sheep have revealed that the administration of salicylates and the resultant inhibition of prostaglandin formation leads to constriction and premature closure of the ductus arteriosus. Pulmonary hypertension follows, creating a significant pressure gradient between the pulmonary artery and the aorta. If one then infuses prostaglandin E_2 (PGE_2), pulmonary artery pressure will be reduced. The latter study demonstrates that the constriction of the ductus is related to the inhibition of prostaglandin synthesis and not to the direct effect of aspirin itself.[5] Salicylates may also produce a mild increase in systemic vascular resistance, which is potentiated in the presence of hypoxia. Umbilical-placental and myocardial blood flow is also increased. Whereas single doses of salicylates do not appear to affect the fetal pulmonary vessels themselves, prolonged exposure may produce pulmonary arterial hypertension, with an increase in the development of medial smooth muscle in small precapillary pulmonary vessels. Rudolf has also pointed out that in the fetal lamb the administration of nonsteroidal antiinflammatory compounds may produce a marked increase in fetal respiration through effects on the brain stem, the peripheral chemoreceptors, or the cerebral cortex.[5] This increase in fetal muscular activity could lead to an increase in the fetal oxygen requirement.

The effects on the ductus arteriosus and the pulmonary blood vessels produced by inhibitors of prostaglandin biosynthesis are extremely important, for they may block the normal, rapid pulmonary vasodilatation that occurs after birth and may lead to persistent pulmonary hypertension after de-

livery. Perkin has observed that cord blood salicylate levels were significantly higher in infants with persistent pulmonary arterial hypertension.[6]

Other important effects of salicylates that result from their ability to inhibit prostaglandin synthesis include alterations in the onset and duration of labor. Prostaglandins are known to play an important role in the cascade of events leading to the initiation, maintenance, and progression of labor. Lewis and Schulman performed a retrospective study of 103 patients who had ingested at least 3250 mg daily of aspirin during the final 6 months of pregnancy.[7] These patients were matched with women with similar disorders who had not been treated with aspirin as well as a control group. The investigators observed a prolongation in the length of gestation and in the length of labor associated with maternal aspirin consumption. While 42% of the aspirin group had gestations of more than 42 weeks, only 3% of the other groups demonstrated a prolonged pregnancy. The estimated blood loss at delivery was also higher in those patients who had ingested aspirin.

After delivery, maternal aspirin therapy may lead to a higher incidence of neonatal jaundice by decreasing available albumin-binding sites in the neonates.[8]

Over the years, much concern has arisen regarding other effects of aspirin in pregnancy, specifically its teratogenic potential and its ability to affect birth weight and perinatal survival. Aspirin can produce a variety of malformations in animals and can inhibit growth in human cell cultures.[9] However, the study of over 50,000 pregnancies by the Collaborative Perinatal Project failed to demonstrate an increased incidence of malformations in the population using aspirin.[1] On the other hand, one must be concerned about the effects of the interaction of aspirin with teratogens such as alcohol, fever, and infection. An evaluation of the data from the Collaborative Perinatal Project has also failed to demonstrate a decrease in birth weight or an increase in perinatal mortality among patients using aspirin.[10] Although studies by Collins and Turner in Australia describe a decrease in birth weight as well as an increase in the incidence of stillbirth, the patient population examined was small.[11,12] In addition, these patients were extremely heavy users of aspirin, consuming aspirin powders containing between 384 and 510 mg of aspirin 2–12 times daily.[8]

Indomethacin

The nonsteroidal antiinflammatory agent indomethacin has recently been utilized to inhibit premature labor. Studies in Europe and Israel have confirmed the efficacy of this drug as a tocolytic agent.[13] However, several reports have demonstrated the ability of indomethacin to produce premature closure of the ductus arteriosus, with resultant pulmonary hypertension in the newborn.[14–16] Although a prospective randomized double-blind study by Niebyl demonstrated no pulmonary hypertension or bleeding problems among 15 infants exposed to indomethacin in utero,[17] the use of this drug for tocolysis has been largely abandoned in the United States.

Acetaminophen

Acetaminophen is an analgesic, antipyretic medication that lacks antiinflammatory properties. It does not affect the bleeding time, as does aspirin, and it produces less gastrointestinal irritation than aspirin does. The drug crosses the placenta in its unconjugated form. In the study by Rumack, acetaminophen was not associated with an increased incidence of intracranial hemorrhage in premature infants.[4] The drug could theoretically produce fetal hemolytic anemia and methemoglobinemia.[18] Although formal clinical or epidemiologic studies of its use have not been conducted, adverse maternal or fetal effects from acetaminophen have not yet been reported.

Corticosteroids

Considerable concern has focused on the effects of corticosteroids on fetal growth and development and neonatal adaptation. Corticosteroids are well known to induce a number of enzymes in many fetal organs; but, at the same time, they have been found to inhibit cell multiplication, impair deoxyribonucleic acid (DNA) synthesis, decrease brain weight, and decrease the rate of myelination.[19] In animal models, corticosteroids have also produced a decrease in body weight and immune responsiveness, a reduction in placental growth with an associated increase in placental senescence, and an increase in fetal pancreatic islet cell maturation and degeneration. In rodent models, corticosteroids have been associated with an increased spontaneous abortion rate, placental insufficiency, and the induction of cleft palate.[19,20] Few of these effects have been confirmed in human studies.

The most commonly employed therapeutic steroids include prednisolone, dexamethasone, and betamethasone. Each has an 11-beta OH radical responsible for its physiologic activity. The placenta is a rich source of 11-beta-ol-dehydrogenase and is capable of converting the active steroid to its inactive 11-keto form.[21,22] Therefore, the fetus appears relatively protected when such corticosteroids are administered to the mother. Using incubations of term placental tissue, Blanford has demonstrated that approximately 67% of cortisol and 51% of prednisolone are converted to their respective 11-keto compounds.[23] On the other hand, little conversion of dexamethasone or betamethasone was observed. However, placental perfusion studies by Levitz demonstrated that the conversion of the commonly used steroids noted above is approximately the same, with clearance indices of 0.27 to 0.48.[22] After administration of prednisolone to the mother, the maternal fetal concentration gradient is approximately 10:1,[24] whereas the maternal-fetal concentration gradients for betamethasone and dexamethasone are approximately 1:1.[25,26] Prednisolone may, therefore, be a more desirable drug, because the fetal concentration remains significantly lower than that of the mother when it is used.

During pregnancy, two patterns of corticosteroid administration are usually encountered. Corticosteroids may be administered chronically or over several days to induce fetal lung maturation during the early third trimester. Most often, betamethasone or dexamethasone have been used to induce fetal lung maturation. The evaluation of recent data from the Collaborative Group on Antenatal Steroid Therapy reveals that dexamethasone levels in cord vein blood are elevated for 24 hours after administration of a single dose of this drug.[27] Such exogenous corticosteroid administration will also inhibit fetal adrenocorticotropic hormone (ACTH) and stimulation of the fetal adrenal and will lead to a rapid fall in fetoplacental estriol production. Ohrlander reported a significant decrease in amniotic fluid cortisol and a maximum fall of approximately 55% in urinary estriol excretion after a betamethasone load.[28] Estriol levels remained depressed for 13 days. Studies investigating the long-term effects of such corticosteroid therapy have been encouraging. Children studied during the 7th year of life, after the administration of betamethasone to accelerate fetal pulmonary surfactant synthesis, revealed no significant differences in cognitive development or physical growth when compared with a control population.[29]

The chronic administration of corticosteroids has not been associated with teratogenicity in human pregnancies. Specifically, no increase in the incidence of cleft lip or palate has been reported.[30] Whereas neonatal adrenal suppression is a theoretic concern, it has been observed only rarely. On the other hand, Reinisch has demonstrated a decrease in birth weight in the offspring of pregnant women treated with corticosteroids for infertility and subsequent pregnancy maintenance.[31] These women received 10 mg of prednisone per day, and all subsequently delivered full-term infants. A

marked increase in the percentage of infants with low birth weight was observed. Reinisch confirmed this finding through the use of a mouse model. He speculated that corticosteroids might have direct effects upon fetal growth or upon placental development or indirectly affect the fetus through effects on maternal physiology.

Immunosuppressants

Azathioprine

Azathioprine, a derivative of 6-mercaptopurine (6-MP), was developed to delay the rapid in vivo degradation of 6-MP.[32] 6-MP is cleaved nonenzymatically from azathioprine, particularly by the tissue sulfhydryl compounds cysteine and glutathione. 6-MP is then metabolized to its active form, thioinosinic acid. The administration of radioactive azathioprine to the mother at 9, 14, and 15 weeks' gestation led to the appearance of 64-93% of the administered radioactivity in fetal blood 150 to 360 minutes later.[33]

Several concerns have been raised regarding the effects of azathioprine on fetal immunologic function and growth. Whereas the administration of azathioprine to animals has been associated with skeletal malformations, this teratogenicity has not been confirmed in human gestations.[34] However, azathioprine administration has produced neonatal lymphopenia, decreased serum IgG and IgM levels, and a reduction in the thymic shadow.[35] Chromosomal aberrations have been noted in the lymphocytes of these infants but have cleared in 20-32 months.[36]

Scott has emphasized that maternal-fetal immunogenetic disparity facilitates fetal growth.[37] He has observed a reduction in fetal growth in human pregnancies in which the mother received azathioprine.[37,38] In a rat model, Scott confirmed that the administration of azathioprine produces fetal and neonatal growth retardation as well as smaller placentas with a reduced cell number.[37] Whereas the reduction in fetal growth is important, one must also be concerned with the long-term effects of azathioprine. Little information is available on subsequent infection rates, the incidence of cancer, or reproductive potential in human offspring exposed to this drug in utero.

Gold

Gold salts are highly bound and cross the placenta poorly. They should, therefore, theoretically have limited effects upon fetal development. However, experience with their use in pregnancy has been limited; for this reason, they are probably best avoided.[39]

Chloroquine

The antimalarial, chloroquine, is also contraindicated in pregnancy, because it may be associated with chromosomal and retinal damage.[40] Chloroquine binds to DNA and inhibits nucleic acid repair. It has been associated with chromatid gaps or breaks in lymphocyte cultures from patients with rheumatoid arthritis who are receiving this drug.[41] In the mouse fetus, chloroquine has demonstrated a strong affinity for the pigmented epithelium in the retina.[42] It might, therefore, produce visual defects which would not be appreciated until later in life.

Conclusion

In pregnancies complicated by autoimmune diseases, the drugs presently available can provide great maternal benefit with comparatively limited fetal risk. Corticosteroids, once used with great caution for fear of their teratogenic potential, have been associated with few untoward fetal effects. Salicylates, on the other hand, have been administered freely. Yet their ability to inhibit prostaglandin synthesis may produce marked changes in fetal circulation and neonatal hemostasis.

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