THE EFFECTS OF MATERNAL MEDICATIONS ON THE FETUS AND NEWBORN *

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Following the recent therapeutic mishaps involving the unborn fetus and the newborn infant, climaxed by the outbreak of thalidomide embryopathy, numerous articles about the adverse effects of various maternally administered drugs to the developing fetus have appeared in the medical literature.[1-7]

Sometimes an unequivocal relation between a maternal drug and a fetal effect has been established but, more often, and particularly in recent years, we have been in an era when perhaps too much speculation is occuring regarding the relation of a given drug to the production of a fetal anomaly which may well have occured coincidentally. Recent surveys revealed that the etiology of approximately 90 per cent of human congenital malformations remains unknown,[8] although 92 per cent of women received one or more drugs during their gestation.[9] A certain percentage of human pregnancies will inevitably result in the birth of an abnormal fetus, due to either genetic or environmental disturbances unrelated to the drugs which the mother may have taken during pregnancy. Between the recent alarmist approach and the complacent attitude of the past, a critical alertness by the physicians should be the chosen course of action.

The purpose of this report is to briefly review the accumulated information on the various medications which, when administered to the mother, have an effect upon the fetus and neonate.

Physiologic and Pharmacologic Considerations

The placenta is a complex organ accomplishing a multitude of functions through a variety of mechanisms.[10] Drugs that have a molecular weight of less than 1.000 can usually cross the placenta with ease. The following mechanisms are currently accepted as significant in the transport of substances across the placenta:[11-13]

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1. *Simple diffusion :* Substances concerned with the maintenance of biochemical homeostasis (e. g. water, electrolytes, amines, oxygen, carbon dioxide.)
2. *Facilitated diffusion (carrier system) :* Substances concerned primarily with fetal nutrition (e. g. natural sugars and amino acids, most of water soluble vitamins.)
3. *Active transport (enzymatic) :* Certain inorganic ions, endogenous substrates and rare foreign compounds.
4. *Special processes :* Substances of immunological importance only. Pinocytosis is the process by which microscopic invaginations of the villi engulf tiny droplets of plasma and discharge them into fetal circulation at a relatively slow rate.[14] Leakage due to minute breaks in the placental villi has been implicated as a route of transfer of intact blood cells to the fetus from the maternal circulation.[15 - 18]

Foreign compounds cross the placental barrier almost purely by simple diffusion, except the antimetabolites which closely resemble naturally occuring material and are transported by an active enzymatic process.[10]

Besides the mechanisms of placental transfer, other critical factors in the production of effects on the fetus include: the dosage and duration of therapy, the stage in pregnancy at which the drug is first given to the mother, the state of the mother, particularly her age, parity and nutrition, and the difference in metabolism of certain drugs in the fetus and newborn (pharmacologic and functional immaturity.)

There are several types of fetal effects resulting from maternal drugs which should be considered, such as fetal death, malformations (teratogenic effects), influence on fetal growth, interference with neonatal adjustment, and miscellaneous toxic effects.[7]

Hormones

Sex Hormones : Oral progestins are structural analogues of testosterone.[6] In cases where the mother has been treated with synthetic progestational agents during pregnancy for either habitual or threatened abortion, female infants have been born with masculinized external genitals. Clinically, the infants presented a picture identical to that observed in adrenogenital syndrome. The 17-ketosteroid excretion was, however, not increased (non-adrenal

ERRATA

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p. 81 line 36 should read «intrauterine growth retardation of cyclophosphamide, busulfan and chlorambucilon»

Idiopathic Paroxysmal Myoglobinuria-Ş. Özsoylu and S. Akgün

p. 101 Table 2 change bilirubin 7.0 mg % to 0.7 mg %.

p. 102 In Figure 1 change Berezidin to Benzidin

2. Patient's Hb (preattack) should read Patient's Hb in preattack urine.

3. Patient's (post attack) should read Patient's urine (post attack).

p. 105 line 23 change case to syndrome.

When the use of a folic acid antagonist is contemplated, which has a highly selective toxicity to the developing embryo, a therapeutic abortion should be considered.

Antibiotics and Chemotherapeutic Agents

Antibiotics : Can readily cross the placenta and are found in the fetal blood and in the amniotic fluid. Streptomycin when administered to the pregnant mother can produce ototoxicity (eighth nerve damage) in the infant in utero.[47] Nevertheless because of its efficacy in the treatment of tuberculosis its administration should not be withheld when it is clearly indicated, but should be used with the awareness of the potential fetal toxicity.[7] Animal teratogenicity has also been reported.[48] Tetracyclines administered to pregnant women late in gestation may be deposited in growing bones and temporarily decrease bone growth in premature infants. They can also cause discoloration and enamel hypoplasia of deciduous teeth in infants.[49 - 52] The degree of discoloration or hypoplasia is a function of the dose of the drug.[53] Studies indicate that dental abnormalities are produced in the teeth which are undergoing mineralization at the time of tetracycline administration. The abnormality, not apparent at birth, becomes obvious with eruption of the teeth, and may be a serious cosmetic handicap. The involved teeth are usually of a yellow color and can be distinguished from other types of teeth-staining or hypoplasia of the enamel by the brilliant fluorescence seen in ultraviolet light. Exposure of the teeth to the sunlight results in a gradual change to a brown color with concomitant loss in fluorescence.[6] Although when tetracycline is given to the mother, no abnormalities, in permanent dentition have been described, the permanent teeth may well be affected if the drug is administered to children during the period of odontogenesis.[6] Reports of animal teratogenicity appeared in the literature.[54] Knowledge of these fetal effects of maternal tetracycline may temper the decision to use this drug in pregnancy.[7]

The newborn infant, and especially the premature, is very susceptible to chloramphenicol because it is unable to conjugate and detoxify this agent due to functionally immature liver.[5, 6] High blood levels of free chloramphenicol may result from conventional therapeutic doses.[55] Cases of neonatal chloramphenicol toxicity (gray syndrome) have been reported.[56] The clinical findings consisted of ashen gray cyanosis, hypothermia and flaccidity, indicating cardiovascular collapse, followed shortly by respiratory failure and card-

iac arrest. It has been recommended that daily doses for full term and premature infants not exceed 50 and 25 mg/kg respectively.[6] Novobiocin is an inhibitor of the enzyme glucuronyl transferase and, therefore, interferes with the excretion of bilirubin via the bile, causing, thus, hyperbilirubinemia and jaundice.[57, 58] Nitrofurantoin (Furadantin^{R}) may cause hemolysis and jaundice in infants with glucose-6-phosphate dehydrogenase deficiency.[59] Kanamycin can produce renal toxicity, usually reversible, transient vertibular injury, manifest with vertigo, and permanent inner ear deafness (eighth nerve damage).[60] Since all these compounds cross the placenta with relative ease, caution should be exercised in their use during the perinatal period. To date there have been no reports of fetal damage or neonatal toxicity due to penicillin or erythromycin.

Sulfonamides : Can pass easily the placental barrier and enter the fetus, and, therefore, caution should be exercised when these drugs are given to the pregnant woman near term.[61, 62] It has been shown that sulfonamides compete effectively with bilirubin for binding sites on serum albumin and displace protein-bound bilirubin. The increased amount of free bilirubin is then available for diffusion into the tissues, including the brain, thus increasing the risk of kernicterus.[61, 63] It is also known that sulfamethoxypyridazine can produce hemolysis and jaundice in newborn infants deficient in erythrocyte G-6-PD, if the drug has been administered to the mother prior to delivery.[64] When labor is imminent and especially if the fetus is premature, maternally administered sulfonamides, particularly long-acting ones, should be discontinued.

Isonicotinic Acid Hydrazide (INH): Readily crosses the placenta. In view of the known toxic side effects of this drug on the central nervous system and other vital organs, it seems advisable to bear in mind the possible hazards to the fetus of prolonged exposure.[12, 65]

Antimalarial Drugs : Quinine is a well known abortifacient and may cause fetal death.[7] Fetal thrombocytopenia has also been reported.[66] The mechanism of this immunological phenomenon has recently been elucidated as a transplacental passage of both antibody and quinine.[67] Fetal ototoxicity was suspected as early as 1870[68] and confirmed later clinically[69] as well as experimentally[70] as the result of damage to the inner ear of the fetus. Chloroquine may cause nerve deafness in the fetus when administered to the mother, a side effect which has been noted in adults too. The fetal ototoxicity may, at

times, be associated with malformations or death.[71] Therefore, the use of these drugs during gestation should be avoided whenever possible.

Metronidazole (Flagyl) : Although it has been administered during pregnancy for trichomonal vaginitis without any observed adverse effects to the fetus,[72] caution should be exercised in its use to the pregnant woman or nursing mother since the drug crosses the placenta rapidly and is also excreted in the breast milk.

Antithyroid Agents

The human fetal thyroid concentrates iodide at 14 weeks gestation[73] and is able to synthesize organic iodine compounds at 15 to 19 weeks pregnancy.[74] Therefore, antithyroid medications administered to the pregnant mother beyond the first trimester may interfere with fetal thyroid function.[7]

Thiouracils,[75] imidazoles,[76] iodides,[77] radioactive iodine[78] and perchlorates[79] cross the placenta and may produce compensatory enlargement of the fetal thyroid, secondary to inhibition of thyroxin production, with resultant increase in pituitary thryoid-stimulating hormone. Thiouracils given to the pregnant woman with thyrotoxicosis may produce a goiter in the fetus which persists for several months postnatally and regresses spontaneously. The effects of such a fetal goiter may be either mechanical (face presentation at delivery due to inadequate flexion of the head or tracheal compression and respiratory distress) or functional (infantile hypothyroidism.) It has been suggested that the development of a fetal goiter is related to the amount and duration of maternal dosage[1] and, therefore, if these drugs have to be used during pregnancy the minimum effective dosage should be utilized. Also, breast feeding is not advisable, as thiouracil is excreted in the milk.[80] Rarely the infant may demonstrate signs of transient hyperthyroidism as a result of withdrawal of the inhibiting drug, and release of the hyperplastic gland.[81] Iodides also may produce goiter in the newborn. Although clinical hypothyroidism in the infants is rarely seen,[81] when it occurs it can cause permanent damage.[50] Therefore, self medication by the pregnant woman should be avoided.

Radioactive Iodine may cause severe and permanent damage to fetal thyroid, leading to involution, colloid goiter, and hypothryoid-

ism.[78] Therefore, studies for either diagnostic or therapeutic purposes utilizing I^{131} are contraindicated during pregnancy.

Hypoglycemic Agents

Oral Hypoglycemics : In 1960 a possibly teratogenic action of sulfanylurea therapy was reported by Larrson and Sterky.[82] Available data indicates both normal and abnormal infants have been born of mothers who received oral hypoglycemic drugs during pregnancy. In the laboratory malformed fetuses have been produced when pregnant rats received carbutamide, tolbutamide and chlorpropamide.[83] Recently Lucey reported that Phenformin (D.B.I.) increased tissue lactate production and decreased oxygen consumption. This effect was more marked in fetal guinea pig tissue than in adult tissue. He concluded that any substance capable of causing tissue anoxia is particularly dangerous to the fetus.[50] These drugs are no longer recommended for use in the pregnant diabetic.[50]

Insulin : Thus far, there is no valid evidence that insulin, used for the treatment of the pregnant diabetic, has caused any fetal malformations and, therefore, is the drug of choice for the pregnant diabetic woman.[7] Insulin shock therapy for psychiatric purposes is contraindicated during gestation since it can cause fetal loss.[59]

Sedatives

These drugs in this field of therapeutics are mostly used as palliative rather than curative remedies. Therefore, on this basis and because of deficient knowledge in their developmental pharmacology even a marginal fetal risk should not be tolerated.

Thalidomide : The association between the administration of thalidomide to women in early pregnancy and the occurance of fetal malformation has been established beyond any doubt.[84 - 85] The spectrum of abnormalities noted is broad and the most common ones are fetal death, phocomelia and hearing loss. The malformation rate approached 100 per cent when the drug was taken from the 34th to to the 45th day after the last menstrual period, even when it was taken in small doses for short periods of time.[7] The use of drugs such as the antiepileptic aminoglutethimide (Elipten^{R}), the sedative glutethimide (Doriden^{R}) and the stimulant bemegride (Megimide^{R}), which have a chemical formula similar to thalidomide (i. e., containing the glutarimide ring), should be avoided during the first trimester of pregnancy until more knowledge becomes available of their possible effects on the conceptus.

Barbiturates : Pass the human placenta readily.[11, 12] It has been shown that heavy barbiturate premedication can cause neonatal drowsiness to the extent that the infant is unable to establish adequate breast feeding, sometimes lasting up to the sixth postnatal day.[89] Recent work in newborn rodents indicates that the liver of the neonate lacks the microsomal enzyme systems necessary to metabolize drugs such as barbiturates.[90, 91] Excessive amounts of phenobarbital may also cause neonatal bleeding.[59]

Tranquilizers : Although phenothiazines have been suspected as causing hyperbilirubinemia in premature infants, more recent studies were unable to demonstrate such an effect.[92, 93] The possibility of long term behavioral changes in the offspring of mothers treated with meprobamate has been raised.[94] Phenothiazine as well as meprobamate reduce the amount of analgesic or sedative medication needed during labor.[12, 95, 96] In a recent study it was shown that chlordiazepoxide (Librium^{R}) administered intramuscularly to pregnant women during the first stage of labor crosses the placental barrier but has no depressing effect on the newborn infant.[97] Reserpine can produce a non-infective nasal discharge and lethargy in infants of mothers treated with this drug within two days of delivery.[98] Nasal congestion may be present as long as the sixth postnatal day.[12] Belladonna derivatives, atropine and scopolamine, cross the placenta and can cause mydriasis in the newborn.[12] Administration of atropine to the mother may produce fetal tachycardia detectable by means of fetal electrocardiogram.[99] Similarly, maternally administered atropine may inhibit fetal gastrointestinal motility and result in paralytic ileus in the newborn. Paraldehyde can be detected on the breath of the neonate if the mother received this sedative during labor, causing neonatal depression in a large percentage of infants.[100] Chloral hydrate should not be used in premature deliveries. The drug readily passes the placenta and in premature infants who do not yet have a fully developed glucuronic acid conjugation mechanism it can not be properly detoxified.[12] Ethyl alcohol traverses the placenta with no evidence of neonatal depression regardless of the state of maternal inebriation.[101]

Several other drugs in the category of antihistaminics, antiemetics and antidepressants have been suspected as causing embryopathy, e. g. meclizine (Bonine^{R}) cyclizine (Marezine^{R}), chlorcylizine (Perazil^{R}), phenmetrazine (Preludin^{R}), and imipramine (Tofranil^{R}). Although the proof is inconclusive, nevertheless caution should be exercised in the use of these drugs during pregnancy.[7]

Analgesics and Anesthetics

Opiates : Morphine and meperidine are the most commonly employed narcotic analgesics in obstetrics. Both of these agents readily pass the placenta and can be the cause of severe respiratory depression when administered to the mothers during labor or delivery.[7, 12] Narcotic antagonists (nalorphine, levallorphan) are effective in preventing narcotic depression in the newborn by administration to the mother before delivery.[102] They, at the same time, are themselves respiratory depressants and should, therefore, not be used in babies depressed for other reasons.[6] These drugs have also been found to reduce the attentiveness of the newborn.[103] Pinpoint pupils and withdrawal symptoms have been observed in infants born to mothers addicted to morphine or heroin.[104] They have also been reported in offspring of pregnant women under prolonged medical treatment with tincture of opium and meperidine[105] and codeine.[106] These symptoms can be diagnosed in utero, may be present at birth or appear as late as the fourth day. The withdrawal syndrome may result in increased fetal movement or occasionally death in utero; whereas in the newborn it is characterized by restlessness, hyperirritability, dyspnea and cyanosis, vomiting and poor feeding, diarrhea, yawning and stretching, sweating and fever, pallor, tremors and rarely convulsions and death. Therefore, its prompt recognition with institution of therapy is necessary. Sudden withdrawal effects may be precipitated in addicted infants by nalorphine administration.[7, 12, 104]

Non-Narcotic Analgesics : Salicylates in large amounts may cause neonatal bleeding.[59] They may also compete with bilirubin for binding sites on serum albumin, displace protein-bound bilirubin and thus facilitate the diffusion of free bilirubin into tissues accelerating the development of kernicterus.[6] Their animal teratogenicity has been established.[107] Phenacetin may produce methemoglobinemia, sulfhemoglobinemia as well as anemia.[6, 108] Dextropropoxyphene (Darvon^{R}) has not been reported to be injurious to the fetus when given to the pregnant woman.

Anesthetic Agents : Most general anesthetics exert a depressant effect upon the fetus. The degree of narcosis of the newborn is usually proportional to the depth and duration of maternal anesthesia.[12, 94] It has also been demonstrated that respiration is more prompt and efficient in newborns delivered under spinal than under general anesthesia.[109] A fetal complication of maternal caudal an-

esthesia with mepivacaine during labor has recently been reported. The babies, if not stillborn, manifested bradycardia and, at times, convulsions and death. The cause of the syndrome is reported as accidental introduction of the drug directly into the fetus.[110] Accumulated data suggest caution in employment of elective surgery in early pregnancy lest anesthetic agents might possess teratogenic activity and indicate the need for further research in mammalian systems.[6]

Miscellaneous Agents

Viruses : Transfusion of whole blood or infusion of pooled plasma to the mother may cause intrauterine transplacental transmission of the virus of serum hepatitis and produce neonatal jaundice and later cirrhosis.[111, 112] Therefore, it is of paramount importance to eliminate any donors with history of jaundice since viremia capable of producing serum hepatitis is present for long periods of time in apparently healthy people. Small pox vaccination is a well-documented viral hazard to pregnacy, which can cause widespread visceral and cutaneous vaccinia and fetal loss.[113, 114] Primary smallpox vaccinations and probably revaccinations should, therefore, be deferred during pregnancy.[25] Oral polio vaccine may occasionally cause viremia in a nonimmune subject and, therefore, the fetus may be exposed when the susceptible mother is vaccinated.[115] Such an instance has recently been reported, in which the mother received Sabin polio vaccine in the second gestational month. The offspring developed a unique intrauterine nephropathy from which he died at the age of three months.[25] Further exploration of possible hazards to the fetus of live virus vaccines administered during pregnancy (influenza oral polio and attenuated measles in particular) is indicated.

Vitamins : Vitamin D ingested in excessive amounts by pregnant women may cause fetal abnormalities such as supravalvular aortic stenosis, peculiar facies, mental subnormality, idiopathic hypercalcemia, diffuse osteosclerosis, nephracalcinosis and failure to thrive.[116, 117] A recent report of the Committee on Nutrition of the American Academy of Pediatrics recommends 400 units of vitamin D per day as optimal intake for normal infants and children, during the last half of pregnancy and during lactation.[118] Vitamin K analogues can cross the placenta and when high doses are given to the mother during labor will increase the risk of hyperbilirubinemia, particularly in the premature baby.[119] It seems likely that the hyperbilirubinemia results from excessive hemolysis. This may be

enhanced by or require the presence of Vitamin E deficiency, abnormalities in the glutathione metabolism of erythrocytes, hypoglycemia and functional hepatic immaturity.[6, 120] Such a reaction has not been noted following the use of the naturally occuring Vitamin K_1.[5, 6]

Anticoagulants : Coumadin drugs (bishydroxycoumarin — Dicumarol[R] and ethyl biscoumacetate - Tromexan[R]) are dangerous in human pregnancy, causing intrauterine bleeding and fetal death.[121] This has occured even with normal maternal prothrombin time.[7] Therefore, whenever there is clear cut indication for anticoagulant therapy during pregnancy it is best to use heparin, which is not only effective but also safe, since it does not cross the human placental barrier.[122]

Thiazides : Thiazides when administered to the mothers during the antepartum period may cause thrombocytopenia in the newborn, associated with scanty megakaryocytes in the bone marrow. At times, this may be accompanied by other evidence of marrow damage, such as a relative diminution in the number of granulocytes and reticulocytes. In these cases the blood may slowly return to normal over six to nine months.[7, 123] Their effects on the serum electrolytes of the newborn have not yet clearly been elucidated.

Hexamethonium Bromide : This ganglionic blocking agent when used in the treatment of hypertension and toxemia in pregnancy may produce paralytic ileus in the newborn.[124]

Protoveratrine used intravenously in the management of eclampsia may cause fetal bradycardia.[125]

Adrenergic Drugs : Fetal bradycardia has been noted after the administration of adrenaline or noradrenaline to the mother.[126]

Cardiac Glycosides : Digitalis crosses the placenta with relative ease, but there is no evidence of any harmful fetal effects.[1]

Skeletal Muscle Relaxants : The placenta is relatively impermeable to the passage of these compounds and, therefore, in usual clinical doses they have no demonstrable effects on the fetus or newborn.[1, 12]

Ammonium chloride which is now rarely used as a diuretic may produce acidosis in the newborn when administered to the mother.[127]

Administration of excessive amounts of hypotonic or hypertonic fluids intravenously to mothers in labor can cause fluid and electrolyte abnormalities in the fetus.[128, 129]

Iophenoxic acid (Teridax^{R}) when administered during pregnancy for cholecystography may cause elevated P.B.I. in the infant.[25, 59]

Smoking : Heavy smoking has been shown to be associated with an increased incidence of low birth weight[130, 131] and prematurity.[132, 133]

Heavy metals taken by the mother accidentally or otherwise may prove damaging to the fetus.[61]

Fluoride crosses the placenta with ease. Prenatal fluoride therapy is reported as of no value because calcification of all the permanent and a large portion of the deciduous teeth is a postnatal process.[134]

Irradiation : There is no longer any doubt but that ionizing radiations can cause embryonic or fetal death and produce in the survivors certain congenital anomalies such as cataracts, tumors, leukemia, stunting, and shortening of life.[135, 136]

General Conclusions

The pharmacologic response of the fetus and newborn cannot be extrapolated from drug therapy applicable to older children and adults. The spectrum of fetal responses to maternal medication may vary, according to gestational stage, from death (in very early embryonic life), malformation (during organogenesis) to perinatal toxic reactions and morbidity (late in pregnancyy or during labor). If the precept of *primum non nocere* is to be followed, careful consideration should be given to the fetus when prescribing drugs to the pregnant woman. A general rule should be to use as few drugs as possible during pregnancy and only with unequivocal indication.

Although the final proof of human teratogenicity of drugs should be sought in man,[137] continued efforts to find out which species or strain of animal is nearest to man, or which combination of species and strains can be used so the translation of results to man is less uncertain than at present, are indicated.[138, 140]

Our knowledge of human developmental pharmacology lags behind the pharmaceutical advances, and, therefore, the alert clinician still constitutes the infant's first line of defense and one must be very careful in observing babies born to mothers who have received new drugs. Observations, studies, and reporting on these infants, along with a program to inform all women of child-bearing age

of the hazards of self-medication, may yield valuable information and help in the reduction of wasted pregnancies and handicapped children.

Addendum

A recent publication (H. R. Shickey : JAMA 196:418, 1966) states that masculinization of the female fetus can be caused by anabolic steroids when administered to the expectant mother particularly during early pregnancy.

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