Drug Risks in Pregnancy Revisited

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In the important interface of assuring safe care for the pregnant mother and her developing child that falls to the family physician, current knowledge of drug risks in pregnancy is essential. A recent survey showed that an average of 4.5 drugs are taken throughout the pregnancy. Eighty percent were self-prescribed, and a positive correlation was shown between the incidence of congenital anomalies and drug intake. Numerous recent reports of previously unrecognized fetal complications of commonly prescribed and self-used drugs and heightened public awareness makes it imperative that family physicians know the risk principles of major drug groups and be able to recognize drug-induced symptoms and signs in the older infant as well as in the newborn.

The discovery in late 1961 of the teratogenicity to the human fetus of thalidomide, a drug first marketed in 1956 in Germany and later available non-commercially in the United States, was a landmark. A direct outgrowth of public concern over the thalidomide disaster,[1] the Harris-Kefauver Law of 1962, henceforth accorded the Food and Drug Administration the responsibility of deciding on the safety and efficacy of a drug. A demand for sufficient observation of performance and testing before a drug would be allowed widespread usage in the United States was codified in law.

Where are we in 1977 after a decade and a half of stringent controls on new drug introduction? There have been no mishaps to equal the thalidomide incident, but there have been numerous cautionary observations of newly recognized fetal abnormalities from older drugs. Have controls been effective or have we been unnecessarily deprived of life-saving drugs as some critics believe?[2] Unquestionably, we have seen the introduction of fewer major drugs. The United Kingdom has often been the site for the introduction of new drugs,[3] and clearly the experience gained there has been taken into account here as we have benefited from their trials. Most new drugs introduced in the United States have not been approved for usage in pregnancy, and Food and Drug Administration procedures exclude pregnant women from control studies. Conceivably, apart from foreign reports and those noted inadvertant untoward effects on the fetus provoked by drug intake in a woman who did not know that she was pregnant, a drug hazardous only to the human fetus could gain approval for usage in the United States.

The test of time inherent in obtaining FDA approval for new drug usage is difficult for many clinicians to endure, particularly experts in various clinical fields who may be thoroughly convinced of the virtues of a particular drug. Often consigned the care of especially difficult cases through their recognized expertise, they resent restriction of healing tools by committees of medical scientists who are not yet convinced of the value or safety of a drug. They argue that provisional approvals could allow the exploitation of an apparently useful drug for difficult patient care problems without allowing sales promotion efforts to be made until approval was accorded on the basis of longer patient care experience and research.

This communication is intended to call attention to drugs currently implicated in fetal deformation or other injury and to some of the newer recognized constellations of fetal abnormalities associated with older drugs.[2]

The Diversity of Drug Intake during Pregnancy

A recent American survey of drug therapy in pregnancy disclosed an average of 4.5 drugs taken throughout pregnancy – 80 percent of which were self-prescribed. Not surprisingly, vitamins, analgesics, and iron were the most frequent followed by antacids, antiemetics, barbiturates, and antibiotics. In the first trimester, hormones, antihistamines, and other drugs were more prominent. A small group of women were found to have received ten or more drugs. The same survey supported other studies in documenting a definite correlation between drug intake in pregnancy and the presence of congenital anomalies in the infant.[4]

The fetus will be reached by most of the drugs taken by its pregnant

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mother. Whether the effect will be nil or disastrous, the *teratogenic potential* depends on the *timing of administration,* the *dose given,* the *duration* of exposure, and the *genetic disposition of both mother and fetus to respond to the drug in question.*

In consideration of fetal development, the first two weeks after conception, the pre-implantation period, is when the fetus is most susceptible to severe damage and abortion. Thereafter, from the second to eighth week, when the basic organ systems are being created, the fetus is extremely sensitive to deformation. Thalidomide is apparently harmless to the fetus unless taken from the 28th to the 42nd gestational days – a critical two weeks. A spectrum of minor and major effects is possible. Some drugs are dangerous through the entire pregnancy and must be avoided, while some may be nearly harmless to the baby's development, but may jeopardize its survival as a neonate. The best way, in theory at least, is to avoid giving all drugs to pregnant women. A compromise is often necessary to assure the health of a woman who may have entered pregnancy with chronic medical problems or who may develop acute problems during the pregnancy. Counseling mothers to avoid self-prescribing and an understanding by physicians and nurses of the risks of certain drugs in early pregnancy are good beginning points for the prevention of unnecessary fetal deaths and deformities.

The first eight weeks of the pregnancy are the most dangerous. Drugs and immunizations should be avoided whenever possible during this period.

The Exogenous Sex Steroids: Oral Contraceptive and Therapeutic Agents

The use of exogenous estrogenic and progesteronal substances in medicine is widespread and increasingly controversial. Although pregnancy testing, supportive hormone therapy, and efforts to increase fertility and alter outcome in mothers with persistent fetal loss and premature deliveries are important usages, the most widespread use of exogenous sex steroids is in contraceptives. Growth in their use during the past two decades has been incremental and the variations in dosage and combination numerous. Apart from subjective complaints, some as serious as thromboembolic phenomena, the list of known fetal effects is lengthening. Masculinization of the fetus after the mother receives oral progestin is known to occur.[5] Long-term behavioral changes have been associated with perinatal hormone administration.[6] Mothers have been shown by Janerich and others to be likely to become pregnant after discontinuing oral contraceptives.[7] There may be a continuing drug effect on the young fetus at its earliest stages. Occasionally, the agents are taken during early pregnancy by mothers unaware of the inception of pregnancy, a usage associated with an increase in cardiac and other congenital anomalies on a low, but definite risk basis.[8] New York State data from 1963 to 1967, after the thalidomide disaster[9] responsible for a brief increase in limb reduction defects, disclosed a fall in total malformations of about six percent whereas the rate of limb reduction defects had increased by a third.[7] Oral contraceptive use increased substantially during these years. An interesting aspect of the association of limb reduction defects with oral contraceptive and other sex steroids is the exclusive male sex incidence reported, suggesting a sex-specific effect.[7]

Therapeutic Risks in Treatment of Threatened Abortion and Premature Labor

The problem of pregnancies at a high risk of abortion, premature labor, and the delivery of premature infants of low viability are persistent therapeutic dilemmas. The use of diethylstilbestrol in threatened abortions was popular from 1955 until the early 1970s, when it was shown that in the occurrence of a rare cancer – vaginal adenocarcinoma in young girls – the single common factor was the treatment of the victim's mother during pregnancy with diethylstilbestrol. The incidence of this tragic disease 15 or more years after a brief exposure suggests the caution with which new drugs or old drugs in new usages should be viewed when administered to pregnant women.[10] Recent reports in the efficacy of 17 alpha hydroxyprogesterone caproate in the prevention of premature labor[11] has provoked valid controversy. The estimated 90,000 deaths associated with low birth weight delivery in the United States in the early 1970s[12] suggest the impetus for a continued search of all means to avert premature delivery. The statistically low carcinogenic potential of diethylstilbestrol is equated to that of the 17 alpha hydroxyprogesterones and defended in light of the risk and death rate of early delivery.[11] At this writing its safety in wide usage seems questionable.

Tranquilizers and Antianxiety Drugs

Diazepam

Diazepam (Valium) has become the most commonly prescribed medication in the United States,[13] and perhaps in the world.[14] First used as a tranquilizer and a muscle relaxant and later as an anticonvulsant, it is now frequently used for its calming effects at delivery.

In the management of normal active labor, in a mother who is not receiving the drug chronically, brief usage in lower doses seems comparatively safe. Cree and co-workers report that a total maternal dose of 30 mg or less in the 15 hours before delivery had little effect on the infant's state. Larger doses, however, were often associated with a low Apgar score, apneic spells, poor feeding, hypotonia, general depression, and hypothermia. Further, the infants studied responded abnormally to cold stress.[15]

The widespread chronic usage of diazepam poses different risks. Withdrawal symptoms have now been reported in adults who discontinued diazepam after four to six months usage,[16] and in newborns who manifested tremors, irritability, hyperactivity, hypertonicity, tachypnea, and voracious feeding. The clinical presentation is indistinguishable from that seen in narcotic withdrawal states. The onset has been noted as early as 2½ hours after delivery and as late as the third day, with effects lasting from 4 to 38 days. Phenobarbital has proven useful for calming.[17]

In chronic diazepam usage during late pregnancy, the fetal fat stores become saturated.[15,18] Cord levels have been shown on occasion to be higher than maternal ones, and high dose cases may show a neonatal rise in levels suggesting drug release, or a delayed fall. The active metabolite desmethyldiazepam (70 percent diazepam activity) has been found to remain at a plateau over seven postpartum days.[15] Further, the half-life in near-term infants (54 hours at 28-34 weeks) is much longer than in older children and adults, further delaying elimination.[19] Exchange transfusion is likely to be only partially successful in the removal of these fat soluble substances.[18]

Teratogenic effects have not been reported with diazepam.

Chlordiazepoxide, Meprobamate, and the Phenothiazines

Transient effects observable in the neonate have also been reported with chlordiazepoxide. Placental passage was demonstrated in four deliveries by Cesarean section. Cord levels were substantial and occasionally higher than maternal ones when the drug had been given intravenously in doses of 100 mg 5 to 15 hours earlier. Affected infants show hypotonia, listlessness, reluctant feeding, and hypothermia which may require a week to subside.[20]

Chlordiazepoxide and meprobamate accounted for almost 75 percent of the non-barbiturate tranquilizers that were used for anxiety in pregnant mothers in a large study group of over 19,000 births followed in the early to middle 1960s. When either drug was employed during the first 42 days of pregnancy, the incidence of congenital anomalies was four times higher than paired cohorts receiving no drug. The differing incidence of anomalies in the study and control groups became insignificant when the drug was employed later in pregnancy.[21] The authors noted the hazard of the frequent prescription of either drug for anxiety when it was not yet apparent that the mother was pregnant (ie, in the earliest part of pregnancy when risks of teratogenicity are highest). Milkovich and Van Den Berg remark that use of chlordiazepoxide and meprobamate in women of childbearing age should be scrutinized and that it would be prudent to assure that the woman was avoiding conception before either agent is prescribed.[21]

Chlorpromazine given in maternal doses in excess of 500 mg per day has produced neonatal depression.[22] Alpha adrenergic blocking effects could theoretically interfere with temperature regulation of the newborn. Apt and Gaffney, noting the large number of teratogens affecting the eye, view the preferential accumulation of chlorpromazine in the fetal eye with suspicion.[23,24] Teratogenicity, however, has not been demonstrated with chlorpromazine. Extrapyramidal reactions are occasionally seen with all the phenothiazines and at all ages.

Hydroxyzine (Vistaril, Atarax) seems safe in prenatal usage but research information is sparse.[20]

Tricyclic Antidepressants

The tricyclic antidepressants cannot be recommended until further information is available. Of the three commonly used tricyclic antidepressants – nortriptyline (Aventyl), amitriptyline (Elavil), and imipramine (Tofranil) – nortriptyline has been demonstrated to pass the placental barrier, provoking urine retention in the newborn.[25] This effect has been noted in older children. Imipramine has been implicated but not proven to be a cause of exencephaly, thoracic dysrhaphia, cleft palate, and adrenal hypoplasia.[26] Desmethylimipramine (Pertofrane) withdrawal symptoms in neonates, breathlessness, tachypnea, tachycardia, cyanosis, and profuse sweating have been associated with weight loss and slow recovery.[27]

Non-Prescribed Analgesics, Antacids, and Antihistamines

The intake of aspirin is ubiquitous in the population at large and as many as 80 percent of all pregnant women take aspirin at sometime during pregnancy. A study of 272 consecutive deliveries in a university obstetrics service disclosed that ten percent of newborns had measurable salicylate levels, some above usual adult analgesic levels.[28] While it has been shown to produce congenital anomalies in rats, human experience has not confirmed this experience. Maternal usage in the ten days prior to delivery can, however, provoke platelet dysfunction and mild disturbance of the newborn's clotting mechanism.[28,29] Massive neonatal hemorrhage necessitating transfusion following maternal intake of calcium salicylate during 72 hours before delivery has been reported.[30]

The antihistamines, cyclizine, chlorcyclizine, and meclizine, frequently used as antinauseants in pregnancy, are highly teratogenic in rats. There has been no documentation of teratogenicity in humans but concern is appropriate that these drugs be avoided whenever possible in the pregnant mother.

A higher incidence of congenital malformations than usual was noted in a study of maternal antacid usage during pregnancy. Although there was no specificity of defect in the infants of the study group, until further explorations are performed a cautionary note to avoid antacids whenever possible seems prudent.[31]

Anticoagulants

The use of warfarin anticoagulants in pregnancy for the treatment of thrombophlebitis has been a long accepted practice. The chronic use of anticoagulants in pregnancy has also become more common as women with prosthetic valves survive corrected mitral stenosis and other lesions to carry pregnancies successfully to term. Early reports of fetal deaths and malformations associated with warfarin derivatives appeared in 1970.[32] Recent reports call attention to various facial stigmata, notably hypoplastic noses with narrowed air passages.[33,34,35] Radiologic studies have shown stippling and hypoplasia of terminal phalanges, and stippling and irregularity of proximal bones of the foot.[34,35] The stippling of the epiphyses noted on roentgenograms and the appearance of the infant may

mimic a heritable form of chondrodysplasia punctata, in which epiphyseal and extraepiphyseal calcifications, a flattened and hypoplastic nose, limb asymmetry, rhizomelia, and eye defects are common.[33] The frequency of multiple medication intake in these often-difficult pregnancies may yield abnormalities attributable to drugs other than the warfarin groups.

It would be prudent to avoid, if possible, the use of oral anticoagulants in the first trimester, with substitution of heparin which does not cross the placental barrier if anticoagulation is considered mandatory. The costliness of heparin and the occasional occurrence of alopecia during long usage are worrisome, but pose no fetal risk. In pregnancy management at term, oral anticoagulants are customarily stopped two weeks or so before delivery with substitution of parenteral heparin if anticoagulation is to be continued without interruption. Hemorrhagic disease of the neonate secondary to warfarin anticoagulants can thus be avoided.

Antidiabetic Drugs

The use of oral hypoglycemic agents in pregnancy was widely frowned upon even prior to recent discussions of accelerated vascular disease processes possibly associated with their usage. Chlorpropamide and tolbutamide have both been associated with multiple congenital anomalies when used in early gestation.[36,37] Chlorpropamide taken in late pregnancy has been associated with profound and prolonged neonatal hypoglycemia.[38] Both drugs should be avoided.

Insulin is the preferred antidiabetic drug for pregnant diabetic women. It is more controllable, has no known teratogenic effect in man, and its placental transfer is probably insignificant. In one animal experiment, chickens treated with insulin before hatching have shown caudal regression, or rumplessness. A small number of infants of diabetic mothers are born with a syndrome of mild caudal regression. Such pregnancies, however, yield far more anomalies than occur in nondiabetic gestation.

Table 1. Drugs Carrying the Risk of Deformation (Teratogenicity)

Drug Administered to Mother	Possible Effects on Fetus
Progestogens, estrogens, and androgens	Prolonged use in pregnancy can cause masculinization of the fetus. Adenocarcinoma of the vagina in women of 16 to 20 years of age has been seen when threatened abortion has been treated with diethylstilbestrol. Phocomelia and limb reduction defects, recently linked with oral contraceptive usage.
Barbiturates Aspirin Dextroamphetamine	When administered in the first trimester, there is a low but increased risk of fetal malformation.
Diphenylhydantoin Trimethadione	Increasingly linked with a broad variety of anomalies when employed in early pregnancy.
Meprobamate	When used in the first six weeks of pregnancy, the incidence of congenital anomalies rises significantly.
Trimethoprim-sulfisoxazole	Unproven effects, but the folic acid antagonist contained suggests danger to the fetus.
Antihistamines	Some are teratogenic to animals, but risks are unproven in humans.
Aminopterin Methotrexate	Folic acid antagonists with known risks for congenital anomalies.

*Modified with permission from Catz CS, Abuelo D: Drugs and pregnancy. Drug Ther Bull 4(4):90, 1974.

Digitalis, Antihypertensives, Antiarrhythmia Drugs, and Diuretics

The effects on the fetus of the various cardiovascular drugs are numerous and their interrelationships too complex to pursue in detail in this communication. The principal drug group, the digitalis glycosides, are known to cross the placenta and are thought to produce no untoward fetal effects; but this is presumptive.

Magnesium sulfate is the most commonly used agent in treating toxemia of pregnancy and advanced preeclampsia. With careful usage, it remains reasonably safe if maternal magnesium concentrations do not exceed 6 to 8 mg/100 ml in the presence of adequate renal excretion.[22] A series of 7,000 infants, in which the newborn serum concentrations of magnesium were equal to that of their mothers, showed no ill effect.[39] Excessive levels of magnesium may cause neonatal hypermagnesemia with hypotonia and respiratory insuffiency requiring temporary ventilatory support. In light of the frequency of its usage in large doses and without serum monitoring, magnesium sulfate has provoked remarkably few problems for either mother or newborn.

Hydralazine is perhaps second only to magnesium sulfate in frequency of usage for toxemia of pregnancy. Untoward effects on the fetus have not been reported. Reserpine is remarkably innocuous and, apart from transient nasal stuffiness, rarely causes difficulty in the newborn.

Diazoxide, when used in the mother, has been found in the cord blood at a level of a little less than half the maternal level. Excretion continued in the urine for a week in four children who, subjected to prolonged follow-up, developed alopecia. Another hair abnormality, hypertrichosis lanuginosa, has been reported. Unexpectedly advanced bone age has been observed.[40]

Hexamethonium, a ganglionic blocker has found some use in toxemia of pregnancy and has been found in cord blood. It may cause in the newborn a paralytic ileus which resolves with conservative treatment.[41]

Alpha methyldopa (Aldomet) has not been adequately studied in pregnancy to permit judgments on its safety.

Propranolol (Inderal), a beta-adrenergic blocking agent is finding more usage in pregnancy in treatment of maternal arrhythmias, hypertension, and hypertrophic subaortic stenosis. It has been shown to cross the placenta in intravenous usage.[42] With continuous usage during pregnancy, it is implicated in fetal depression, postnatal hypoglycemia, bradycardia, and intrauterine growth retardation.[43,44,45] Growth retardation, however, is not uncommon in pregnancies marked by severe maternal hypertension and other illnesses, and the disease process rather than the medication could be implicated. Hypoglycemia is apparently caused by the drug's interference with the fall in blood sugar associated with the normal epinephrine-medicated response. Bradycardia, frequently seen with propranolol administration, results from cardiac beta receptor blockage. The pregnancy in which propranolol is continuously employed is appropriately considered to be "high risk" for the infant and close monitoring is advised for early recognition of the metabolic, respiratory, and cardiac complications which may ensue.[43] Since the drug is metabolized by the functionally immature liver, the expected adult three-hour half-life of the drug[45] may be prolonged, explaining the bradycardia and hypoglycemia which may persist beyond the first day of life. Consideration might be given to dose reduction or to brief discontinuation prior to delivery since this might avoid most untoward neonatal effects.

Diuretics

The thiazide diuretics administered to mothers in late pregnancy have been shown to provoke neonatal thrombocytopenia in their newborns, albeit infrequently.[46] An interesting observation in thiazide usage unproven in human pregnancy is the ultimate development of hypertension in mature rats born of pregnancies treated with chronic low doses of chlorothiazide, which is believed due to chronic hypokalemia.[47] Ethacrynic acid and furosemide are potent natriuretics capable of placental passage and can cause symptomatic hyponatremia in the newborn.[48] Both should be avoided in the week prior to delivery, if possible. Both may be ototoxic to the mother. Their ototoxicity is a potential risk to the fetus but has not been documented.

Iodides and the Antithyroid Drugs

The adverse reactions to the fetus of maternal iodide therapy of asthma and other pulmonary diseases are becoming increasingly realized.[49] Iodine drugs taken after the first three months of pregnancy can produce congenital goiter in the infant, occasionally severe enough to provoke death from upper airway obstruction.[50,51,52] In the goitrous patient, thyrotoxicosis is a risk. In the normal patient subject to excessive iodide intake, goiter, hypothyroidism, and hypersensitivity reactions may result, and in both the fetus and nursing infant the maternal risk of iodide therapy is shared.[53] Suppression of organic iodine binding in utero with depression of thyroid hormone synthesis is suspect.[50] Iodides in chronic intake can induce goiter and hypothyroidism in normal children, the mechanism believed to be the impaired release of T4 and blocked uptake of iodine by the thyroid.[54]

A postpartum risk of maternal iodide intake to be considered is its excretion in breast milk which may constitute a long-term risk to nursing infants under treatment self- or physician-prescribed for asthma.[50] The Committee on Drugs of the American Academy of Pediatrics notes the wide advocacy of the use of iodides in chronic asthma, the limited effectiveness of the products in objective studies and the high doses recommended. Suggested *daily* doses for potassium iodide may represent 10 to 30 times the *total* body iodide content! Nutritional requirements of iodine are as low as 0.2 mg per day and intensive therapy in adults may be as much as 300 mg of potassium iodide every two hours.[49]

Many over-the-counter cough mixtures and preparations contain iodine and may not be considered and mentioned to the physician. Their use should be elicited and halted in pregnancy, eliminated in mothers who breast-feed their infants, and used cautiously at all times unless individual efficacy is documented.

In the hyperthyroid mother the course of therapy can affect the fetus. Radioactive thyroid I 131 has also caused fetal cataracts.[23,55] Propylthiouracil or methimazole taken by the mother can provoke neonatal goiter.

Another halide, bromide, has been implicated in profound neonatal hypotonia and depression compatible with many other causes.[56,57] Used in mothers being treated for emotional disorders, and more frequently as a self-prescribed over-the-counter calmant, the bromide ion passes transplacentally with ease. Slow renal clearance has resulted in elevated levels recorded at 69 days of age, thus depression and hypotension may be protracted. As with the iodides, bromide usage may be casual and not mentioned to the physician.

Anticonvulsants in Pregnancy

The use of anticonvulsants during pregnancy presents a worrisome problem, but rarely a therapeutic dilemma, since the decision is infrequently one of suspending treatment in a patient whose convulsive disorder can be controlled.

Anticonvulsants are increasingly implicated as a cause of abortion and fetal defect with a broad range of abnormalities in morphology and effects on performance and development.[58,59] Complicating clear judgments on their individual toxicities are, first, the low incidence of pregnancy complicated by a seizure dis-

order (0.1-0.4 percent); and secondly, the relatively small numbers of epileptic women followed during their pregnancies in control groups.[58] In addition, there is a frequent association of two or more agents to obtain seizure control which may cloud appraisal of a single drug's teratogenicity. In a recent study including 50,591 pregnant women, the 306 women with history of convulsive disorders tended to have other characteristics associated with increased risk of malformations: they were older, gave birth more frequently to stillborn children, and more often had hydramnios. Monson and coworkers remarked that malformations were more often noted in black children and that epilepsy was more common among white mothers, providing a possible negative factor in a clear association of epilepsy and deformities.[60] Two of the more widely used agents with recent further evidence of teratogenicity are discussed.

Diphenylhydantoin

Diphenylhydantoin has for nearly forty years been a mainstay in the treatment of grand mal epilepsy with recognized hematologic, gastric, cutaneous, and central nervous system toxicities. Its congeners are less widely used and, hence, their complications less frequently observed. It is by far the most widely used of long-term anticonvulsants. It is a known teratogen in animals,[61] a folic acid antagonist,[62] and has produced a high malformation rate (61/1000) in 98 children exposed during the first trimester of pregnancy when daily diphenylhydantoin was taken by the mother.[58]

Infants born of mothers receiving diphenylhydantoin have been observed to have hypoplasia of distal phalanges and nails of hands and feet and abnormalities of palmar creases.[63] Facial dysmorphology, including mouth and gum abnormalities, may be striking. Mental retardation and delays in physical development have also been reported. On the basis of epidemiological investigations, mothers exposed to hydantoin regularly during the first three months are apparently at a two- to threefold risk in the overall frequency of single major malformations.[60]

Hill remarks on the mounting information concerning the effect of diphenylhydantoin in the human being, including chromosome breakage, depression of cellular and humoral immunity, induced folic acid deficiency, enzyme induction, altered cortisol metabolism, and carcinogenesis, among others.[58] From a practical viewpoint, it is clear that the majority of infants born of pregnancies in which diphenylhydantoin was employed are free of major defects. In the face of its utility, cautious usage with monitoring of blood levels to minimal acceptable levels consistent with seizure control is recommended.[60]

Trimethadione

This oxazolidene derivative widely used in the treatment of petit mal epilepsy has recently been implicated in abortion and fetal defect.[64,65] Surviving children may show facial dysmorphia including V-shaped eyebrows, low-set ears with anteriorly folded helix, epicanthal and palatal abnormalities. Performance may also be affected by poor speech, psychomotor and statural retardation. Numerous visceral anomalies have been reported in liver, kidney, and heart; and, at the sensory level, both hearing and visual problems have been associated handicaps.[64] Limited data of experience in pregnancy makes it impossible to estimate the true frequency and risk of fetal defect in trimethadione. The physician managing the pregnant mother should determine that the diagnosis of classic petit mal is secure. The disorder is often overdiagnosed and treated without benefit of the distinctive three per second spike and wave tracing.

Barbiturates

Third trimester maternal ingestion of barbiturates may give symptoms in the newborn that are similar to those from opiate withdrawal. Characteristically, symptoms occur later, often after hospital discharge, and are unaccompanied by undernutrition. An infant may appear normal, followed by depression and hyperexcitability of onset as early as 63 hours and as late as one week. Crying, tremors, sleeplessness, sweating, and hyperacusis respond well to paregoric or phenobarbital, but may continue for two to six months. Maternal doses as low as 60 mg/day throughout the pregnancy have evoked withdrawal symptoms in the neonate.[66] Phenobarbital has not been proven a teratogen, but its frequent association as an anticonvulsant in a patient group with a higher than normal incidence of birth and functional defects is cautionary.

Hemorrhagic Disorders Associated with Anticonvulsant Therapy in Pregnancy

A coagulation defect similar to vitamin K_1 deficiency has been recognized in neonates born of mothers receiving barbiturates and the hydantoins as anticonvulsants through pregnancy. Either or both drugs apparently decrease the levels of vitamin K_1 dependent clotting factors. They may provoke a low prothrombin time, low levels of factors II, VII, IX, and X and other abnormalities. Typically, bleeding occurs earlier than with the classic hemorrhagic disease of the newborn, is more severe, and tends to occur in sites unusual for the classic disease such as the pleural and abdominal cavities. Suggested management includes measurement of prothrombin time at birth, and, if ten percent or if there is evidence of bleeding, administration of fresh frozen plasma or fac-

tor concentrates and vitamin K_1 intravenously is indicated.[67]

Common Antiinfective Agents

Penicillin, ampicillin, and carbenicillin are considered safe in pregnancy and can reach therapeutic levels in the fetus.[68,69] Antistaphylococcal drugs such as oxacillin and methicillin are partially bound to maternal serum proteins but cross the placenta and can reach therapeutic fetal levels[70,71] without apparent harm. Dicloxacillin has little placental transfer at term, and cord levels are detectable but low.[72] Gentamicin reaches the fetus at term, but at reduced blood levels. Its known ototoxic effect on the mother has not yet been reported in the infant. The effect on the fetus of kanamycin is at this time uncertain, but its ototoxicity to the mother is well known and a retrospective Japanese study of treated mothers noted deafness in several children. Dihydrostreptomycin is known to provoke deafness in the fetus. Chloroamphenicol can be given to the mother and although some transmission occurs, it apparently does not harm the fetus. Two medications commonly used for urinary tract infections may be troublesome. The nitrofurantoins may cause hemolysis of fetal red cells in G-6-PD dehydrogenase deficiency and the sulfonamides given near term may compete with bilirubin for albumin binding and increase the risk of hyperbilirubinemia.[73]

Trimethoprim-sulfisoxazole combinations pose the additional risk, unproven, of a folic acid antagonist.[48]

Tobramycin, an aminoglycoside, passes the placenta at 8 to 20 weeks and appears in fetal blood and amnionic fluid.[74] Of the cephalosporins, cephalothin is detectable in amniotic fluid 15 minutes after intravenous administration of one gram to the mother, and the level rises for at least the first hour. Cord blood levels may continue to be bactericidal for at least six hours after a one gram maternal dose has been given.[75,76] Its potential for renal toxicity has not been demonstrated in the fetus.

Cephaloridine passes the placental barrier with ease after intramuscular administration. Two grams given to the mother raised cord blood levels to no less than 1.0μg/ml in a controlled series.[77]

Erythromycin crosses the placenta but levels are low in relation to maternal doses, levels of 800 mg or more being required before cord levels are detectable.[78]

Tetracyclines accumulate in the fetal skeleton, may temporarily arrest bone growth, often discolor teeth in the infant when given after the fifth month of pregnancy, and have been incriminated as a cause of congenital cataract; thus, they should not be given to the pregnant mother.[48,73] As a group, the tetracyclines are heavily used for adults and children in nondiagnosed febrile illnesses as well as upper respiratory tract infections, a practice sharply criticized by pediatric drug authorities.[73] Their special risk in provoking renal and hepatic failure in the pregnant mother when the intravenous route is employed is well known and recently, fatal hepatotoxicity has been reported in children as well.[79,80] Rarely a first choice for any but rickettsial diseases, the tetracycline family has little place in the treatment of pregnant women or young children and poses unusual risks to the fetus.[52]

Prescribed and Nonprescribed Narcotics and Nonaspirin Analgesics: Mixed Risks

It has been long known that the newborn infant of a mother, who has either taken narcotics on her own initiative or has received them for obstetric pain, may be born depressed or suffer withdrawal symptoms. The presence of either unexplained depression in the newborn, or agitation and sweating in the first few days of life, should prompt inquiry and, where possible, serum sampling of the newborn. Congenital malformations resulting from narcotics have not been documented. Withdrawal symptoms may follow methadone usage as a heroin replacement in pregnant mothers. These infants may show low birth weights at term and may be stressed by maternal withdrawal symptoms.[48] A higher incidence of "sudden infant death" among the infants of narcotic-addicted women has been reported.[81]

The use of non-narcotic obstetric analgesics, such as mepivacaine and lidocaine, in paracervical anesthesia and continuous caudal anesthesia have been associated with fetal depression and death, or agitation and convulsions. Exchange transfusion has been required to detoxify the infant. Truncal ataxia, dysarthria, and other apparently permanent sequelae five years after delivery have been described in a survivor and attributed to neonatal intoxication by mepivacaine.[82] The increasing acceptance of an unrestricted and usually nonaddictive analgesic, pentazocine (Talwin), as a substitute for meperidine during labor has proven capable of fetal addiction.[83,84] Affected infants exhibit jitteriness, hypertonia, opisthotonus, and inability to feed. Phenobarbital, chlorpromazine, and paregoric have been used in treatment, as in the narcotic withdrawal state in neonates.[83,85]

Social Customs of Varying Risk: Tobacco, Alcohol, Stimulants, and Hallucinogens

In the infants of mothers who smoke there is a greater number of still births and premature births, and increased perinatal mortality, which was first shown convincingly in the British Perinatal Study.[86] The effects of smoking by the mother on the fetus have been under extensive study in the United States for several years. An

Table 2. Practical Considerations in Prescribing Commonly Used Drugs in Pregnancy*

Contraindicated	Administered Under Supervision	Probably Not Contraindicated
Throughout Pregnancy		
Tetracycline analogues	Other antibiotics	Iron and vitamins (recommended doses)
Aminopterin/methotrexate	Anticonvulsants	
Oral hypoglycemics	Bronchodilators	**Occasional Use Only**
Diethylstilbestrol	Selected antiemetics and diuretics	Aspirin (except at term)
Iodides ?	Endocrine drugs	Alcoholic beverages
	Psychopharmalogic drugs	Simple non-absorbable laxatives
Near Term	Heparin	
Sulfonamides	Selected antihistamines	
Novobiocin	Warfarin anticoagulants	
Warfarin anticoagulants		
Salicylates		

*Modified with permission from Catz CS, Abuelo D: Drugs and pregnancy. Drug Ther Bull 4(4):90, 1974.

early observation that the infants of mothers who smoked regularly during pregnancy tend to be smaller – by as much as 300 gm – and shorter, is now well-established. More sinister were reports of a persistent lag in growth, with children remaining smaller than controls at four and eight years, and exhibiting lower reading achievement scores than those seen in children of nonsmoking mothers.[87,88] A well-controlled matched-pair study performed in the United States has confirmed growth retardation of an average of 250 gm and reduced length in surviving infants of smoking mothers. Long-term prognosis, however, was favorable; at four and seven years there were no significant differences in intellectual functions nor in physical measurements.[89] The mode by which tobacco affects the fetus is unclear but, clearly, pregnant women should avoid smoking since the statistical outcome for infants is less favorable from smoking than from nonsmoking women.

Chronic maternal alcoholism has been associated with a range of malformations and intrauterine growth retardation termed "the fetal alcohol syndrome."[69] Microcephaly, short palpebral fissures, severe refractive error, and altered palmar crease configurations may be striking findings. Cardiac anomalies are occasionally noted and the facies may show characteristic abnormalities.[90,91] Withdrawal symptoms may present in the newborn. The occurrence of microcephaly, delayed postnatal growth, and the early mental and motor retardation in 10 out of 11 children studied by Jones and co-workers[92] indicate the seriousness of the problem.

Amphetamines, now in declining licit supply, may be teratogenic and should be avoided by pregnant women. Marihuana is widely used and no substantial studies confirm untoward fetal effects in humans. Animal studies indicating a teratogenic potential are, however, sufficient to recommend avoidance of exposure to marihuana by women who are or may become pregnant.[93] Lysergic acid diethylamide (LSD), in declining popularity among drug abusers, causes in vitro chromosomal breakage. While feared as a teratogen, it has not been a documented cause of congenital anomalies in human beings.

Comment

Pregnancy offers a certain amount of discomfort, a disposition toward some new medical problems, such as urinary infection, fatigue, and the musculoskeletal discomforts associated with changing posture. The mother may be able to accept much of this if she understands that treatment may have unfavorable effects on her baby. With more serious problems such as chronic or life-threatening infection, seizure disorders, or psychiatric aberration, undesirable risks may be unavoidable to maintain the mother's well-being or even her survival.

Carefully drawn prospective studies of drug usage in pregnancy, particularly those in long-term prepaid group health plans with medication protocols, afford new opportunities to study drug risks in pregnancy. Amniocentesis, now frequently done when genetic risks of malformation or disease are exaggerated, affords another occasion for the study of fetal drug handling which should receive further exploration. A high index of clinical suspicion will remain as helpful as it has in the past, when it was discerned that a rising incidence of aplastic anemia was associated with chloramphenicol intake and that phocomelia was linked with thalidomide. Fitch has pointed out that the failure to look for teratogens may result from the unwarranted presumption that teratogens always act bilaterally, noting that animal experiments with acetazolamide and thalidomide have shown strong preferential unilaterality.[94] Non-drug-linked syndromes, too, can be confused with phenotypically similar teratogen-provoked abnormalities as in the Holt-Oram and thalidomide syndromes.[95]

The first two weeks after conception pose the most vulnerable fetal period for severe damage and spontaneous abortion. From the crucial 14th to 56th day of organ development, there may be no awareness of pregnancy; yet live viral vaccines taken prior to a foreign vacation, or a myriad of other medications, generally harmless to the woman, but of definite risk to a fetus, if consumed, may be taken at this time. Thalidomide taken during the 28th to 42nd gestational day, apparently harmless either before or after, left hundreds of crippled survivors.

With care and conservative use of medications, prescribed or self-directed only when there are definite medical indications, the young fetus can be guarded against many known and many yet-unassessed risks. We can use judgment again at delivery, avoiding the unnecessary risks of drugs that may prejudice the infant's survival at life's most dangerous moment and in the days ahead.

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