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FETAL EFFECTS OF MATERNAL DRUG EXPOSURE

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INTRODUCTION

Throughout pregnancy, expectant mothers are exposed to a variety of xenobiotics that may produce either toxic or therapeutic effects in the fetus. Interest in developmental toxicology and teratologic research was stimulated by the recognition of the thalidomide embryopathy in the 1960s. Subsequently, most research related to fetal drug exposure has focused on the toxic effects of these agents. This has resulted in the publication of numerous brief case reports, human epidemiologic studies and laboratory animal research implicating scores of drugs as fetotoxic. Despite the intensity of these investigations, it is remarkable that only a few therapeutic agents have been demonstrated clearly to be associated with adverse fetal effects.

More recent research efforts in fetal pharmacology have been directed toward the study of fetal therapeutics. This follows more than two decades of investigation aimed at improving prenatal diagnosis through a combination of biochemical, cytologic, and sonographic techniques. These procedures have provided a better understanding of the pathophysiology of certain congenital disorders. Thus attempts at therapeutic intervention have followed as a logical consequence.

This review provides a critical evaluation of these two quite disparate aspects of fetal pharmacology. Emphasis is placed on pharmacologic principles that influence the effects of drug exposure on the fetus.

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ADVERSE FETAL EFFECTS

The incidence of prenatal drug exposure is high. It is estimated that ninety percent of all pregnant women take at least one prescription medication regularly, with the average number being between three and five (1). In addition, there is an evergrowing repertoire of environmental, nontherapeutic and illicit agents to which the fetus may be exposed. With increasing xenobiotic exposure it is likely that associated perinatal complications will increase also.

Exposure of the fetus to certain chemical agents may increase the risk of an adverse perinatal outcome. Although studies of fetal malformation have aroused the greatest interest, intrauterine growth retardation, fetal death, and the eventual development of a functional disability are other frequently cited complications.

A major congenital malformation will be present in 2 to 4% of liveborn infants and it is estimated that these malformations may be a leading cause of infant mortality (2). The etiology of most fetal malformations is unknown. Only 1% are thought to be due to drug or chemical exposure (3). While the percentage of fetal injuries due to chemical exposure may appear low, the total numbers can have a staggering impact when the physical discomfort of these children, the emotional anguish of their families, and the social and economic effect of handicapped children on the community are considered.

The Epidemiology of Teratology

Epidemiologic information is a valuable tool in the early identification of possible teratogens. Khoury & Holtzman (4) have identified five parameters that may influence the detection of a new teratogen by a birth defect monitoring system (Table 1). Since few data collection systems are capable of addressing all of these factors many mildly or moderately potent teratogens may be overlooked. At the other extreme, certain types of epidemiologic studies might over-estimate the teratogenic potential of an agent. This is more likely to occur with retrospective studies in which adverse perinatal outcomes may be preferentially reported. In spite of these drawbacks, available epidemiologic information should be considered when assessing a drug's teratogenic potential.

THALIDOMIDE AND LIMB REDUCTIONS Identification of the thalidomide embryopathy exemplifies the usefulness of epidemiologic data. After demonstration in 1956 of the sedative effects of thalidomide, commercial use steadily increased with approximately one million tablets being sold daily in West Germany by 1961 (5, 6).

The incidence of limb reductions also followed a steady increase, starting

Table 1 Parameters affecting birth defect monitoring systems[a]

1. The frequency with which exposures to the suspected teratogen at the critical stage of development occur
2. The strength with which the drug exerts its teratogenic effects
3. The proportion of exposed fetuses that will be affected by the suspected teratogen
4. The incidence of a malformation within the general population
5. The size of the population to be monitored

[a] Adapted from Khoury & Holtzman (4)

eight to nine months later. The presence of an epidemic was recognized approximately one and a half years after the increase in births complicated by limb reductions. In Hamburg limb reductions increased from 0.2 per 1000 in 1958 to 0.6, 1.3, and 2.7 per 1000 in 1959, 1960, and 1961, respectively (5). After the recognition of the epidemic another six months passed before the association with thalidomide was documented (7). Thalidomide was withdrawn from the German market in November, 1961, with the incidence of limb reductions peaking at 3.1 per 1000 in the first half of 1962 and then falling to 0.5 and 0.2 per 1000 in the second half of 1962 and 1963, respectively (5).

Several factors contributed to the rapid recognition of the teratogenic potential of thalidomide. The chances of fetal exposure were increased by its widespread use among pregnant women in certain geographical areas, such as West Germany. In addition, the risk of developing the thalidomide embryopathy following in utero exposure was between one in two and one in ten (8). Finally, in utero thalidomide exposure resulted in malformations that were extremely rare in the general population. The incidence of limb reductions varies between 1 in 20,000 to 100,000 with tetraphocomelia not being documented prior to 1958 (9).

These factors made possible the identification of thalidomide as a teratogen within a relatively limited population group. Khoury & Holtzman (4) predict that only 1000 exposures would have been required to recognize the thalidomide embryopathy with the present monitoring systems. Unfortunately, there were no birth defect monitoring systems in place at the time of this epidemic, resulting in an estimated 7000 cases of thalidomide embryopathy (7).

VALPROIC ACID AND SPINA BIFIDA Valproic acid is a less potent teratogen, and, consequently, more sophisticated data collection systems were required to identify an associated embryopathy. The association between in utero exposure to valproic acid and the development of spina bifida was first recognized by the birth defects monitoring system of the Rhone-Alps region of France. Between 1979 and 1982, nine of 72 children with lumbosacral neural tube defects were reported to have been exposed to valproic acid in

utero (10). This association was subsequently confirmed through the combined efforts of other birth defects surveillance systems evaluating data over an eleven-year period (11–14). These studies demonstrated the risk of neural tube defects, particularly spina bifida, in exposed fetuses to be between 1 and 1.5%. This is significantly greater than the incidence of 0.35% in neonates exposed to other anticonvulsants or 0.1% in the general population (13, 14).

ANTICONVULSANTS When investigating a suspected teratogen it can be difficult to differentiate the possible teratogenic effects of a drug from those of the disease necessitating the medication. This has been particularly true in determining the fetal risk associated with anticonvulsant use by the pregnant epileptic. Determining the risk of in utero exposure to individual anticonvulsant agents is complicated further by the frequent use of polydrug therapy and the small size of the monitored population.

It has been demonstrated clearly that the offspring of epileptic women have a higher rate of malformations and intrauterine growth retardation than the general population (15–19). However, an increasing number of studies demonstrate a higher incidence of malformations in the offspring of treated compared with untreated epileptics. The total malformation rate in untreated epileptics is reported to be between 2 and 5%, only slightly higher than the general population. In contrast, 6 to 11% of the offspring of treated epileptics show some developmental abnormalities (17, 20). Major malformations increased from none in untreated epileptics to 7.7% in treated epileptics (21) with facial clefts occurring 4.7 times more frequently than in the general population (22). In these studies, polydrug therapy is common and virtually every anticonvulsant has been implicated as a teratogen even though the effects of individual agents are difficult to assess.

The Principles of Teratology

Epidemiologic data provides an assessment of the risk of malformation associated with in utero exposure to a xenobiotic. The developmental toxicity of many agents has been implicated on the basis of case reports and requires further confirmation either by controlled animal studies or extensive epidemiologic evaluations. Although the suspicion of teratogenic potential may be high, warranting their cautious use during pregnancy, one should also avoid prematurely categorizing a potentially valuable therapeutic agent as contraindicated during pregnancy.

A teratogen is an agent that can result in a physical malformation when maternal administration results in significant fetal exposure during the period of organogenesis. Malformations, as defined by Spranger et al (23), are morphologic defects that result from an intrinsically abnormal developmental process. That is, the tissue or organ system affected is altered early in

Table 2 The general principles of teratology[a]

1. Teratogenic susceptibility exhibits genetic variability
2. Phenotypic expression depends on exposure during a critical period of development
3. A teratogen exerts its effects through specific interactions at the cellular level
4. Fetal demise, malformation, growth retardation or the eventual development of a functional disorder are the final results of fetal injury
5. Exposure of the fetus to a teratogen is dependent on the physical properties of the agent
6. A dose-response relationship exists with increasing doses resulting in increasing fetal compromise

[a] Adapted from Wilson (26)

embryogenesis and, therefore, never has the opportunity to develop normally. However, the term teratogen has been applied to almost any drug-related perinatal complication. This has resulted in some confusion when discussing teratogenesis. Iodides, for example, are not classic teratogens as the fetal complication, goiter, would be better described as a toxic or dysplastic reaction. Some of the fetal abnormalities associated with exposure to cocaine, such as asymmetric limb reductions, are probably due to vascular compromise of an otherwise normally developing extremity (24, 25). These defects would therefore be described as disruptions, not malformations.

To assist in identifying chemical agents as teratogens, Wilson (26) has proposed a set of general principles (Table 2). These principles provide a framework within which the teratogenic potential of an agent can be studied. While several agents have been described as "known" human teratogens (Table 3), it is doubtful whether any of these truly fit Wilson's model. The available information is even less definitive for a number of other therapeutic agents suggested as possible human teratogens (Table 4).

GENETIC INFLUENCE ON TERATOGENESIS The first principle of teratology indicates that some individuals may be more likely to develop a malformation

Table 3 Drugs considered to be known teratogens

	Teratogenic principles demonstrated					
Drug	1	2	3	4	5	6
Ethanol	–	+	–	+	+	+
Phenytoin	+	+/–	+/–	+	+	+
Valproic Acid	+	·	·	+	+	+
Retinoic Acids	·	+	·	+	+	+
Warfarin	·	+	·	+	+	–
Thalidomide	–	+	–	+	+	·
Methotrexate	–	–	+	+	+	–

Table 4 Drugs suspected to be teratogenic

Drug	Suspected Malformation	Reference
Cocaine	Cardiac, skeletal, renal	27, 28
Lithium	Cardiac	29
Heparin	Facial, optic, skeletal	30, 31
Benzodiazepines	Craniofacial, palate	32–34
Phenobarbital	Palate, craniofacial	16, 17
Tetracycline	Skeletal	35
Carbamazepine	Craniofacial	36, 37

when exposed to a teratogen, that is, they are susceptible to the morphogenic effects of that agent. This susceptibility is determined by the individual's genotype and is therefore an inherited quality. Susceptibility and resistance are modulated through specific mechanisms (Table 5). Each one of these mechanisms may vary in activity among individuals and may be inherited in a different fashion. Therefore, while two individuals may both be resistent to the embryopathic effects of an agent, this resistance may be due to different mechanisms.

Phenytoin Interindividual variability in the expression of the fetal hydantoin syndrome has been noted since the first descriptions of this syndrome were reported (38). The syndrome occurs in 5 to 10% of exposed fetuses and typically consists of minor facial and digital anomalies, growth deficiencies, and mental retardation (20, 39). Even within the group of affected individuals, there are differing patterns of malformation (38). Bustamente & Stumpff (40) reported trizygotic triplets exposed in utero to phenytoin, each with a different pattern of malformation. This is supported by another report in which differing patterns of malformation were demonstrated in four brothers all of whom were exposed to phenytoin in utero (41).

This genetic variability has also been demonstrated in animal model systems. Finnell & Chernoff (42) reviewed previously reported data on fetal malformations in three inbred strains of mice, namely SWV, C57BL/6J, and

Table 5 Possible mechanisms of genetic variability

1. Interindividual differences in drug-receptor interactions
2. Interindividual differences in drug biotransformation to either reactive intermediates or inactive products
3. Variations in mechanisms of cellular repair
4. Differences in the inherent structural stability of the development of specific multicellular organs

C3H/IgMI mice. They found considerable variation in the mouse fetal hydantoin syndrome among these strains. All three strains had a high rate of anomalies of the distal phalanges. However, the SWV mice more frequently had renal, digital, vertebral, and cerebral ventricular anomalies. The C57BL/6J mice had a higher rate of occipital, facial, and ocular malformations.

There also appeared to be a strain difference in the dose dependency of these malformation rates. For example, at the highest dose, 60 mg/kg, dilation of the cerebral ventricles was more common in the SWV mice (68%) than in the C3H/IgMI or C57BL/6J mice (32 and 30%). When a lower dose was used, 20 mg/kg, the incidence of cerebroventricular dilation was similar for the SWV and C3H/IgMI strains (27 and 20%) but higher than the incidence in the C57BL/6J mice (8%).

In humans, attempts have been made to find a marker that would identify the fetuses at the greatest risk for developing the fetal hydantoin syndrome when exposed to phenytoin. Two groups have attempted to correlate an increased risk for phenytoin-associated malformations with an inherited inability to detoxify reactive intermediates during phenytoin metabolism (43, 44). However, neither of these has directly demonstrated differences in metabolism. Moreover, Hansen & Hodes (45) were unable to demonstrate any qualitative or quantitative differences in metabolite production between highly resistant and susceptible strains of mice following pretreatment with phenytoin for 24 hours.

Valproic acid One of the proposed mechanisms for genetic predisposition to developmental toxicity postulates that certain individuals possess "liability genes" (26, 42). This implies that, in these individuals, a particular malformation is more likely to occur spontaneously and that exposure to certain xenobiotics may cause the same malformation. Therefore, while an agent-specific syndrome may be present, other less specific malformations may also occur.

Valproic acid may be associated with a constellation of minor craniofacial and limb anomalies, constituting a "fetal valproate syndrome" (46, 47). However, unrelated to this sndrome, there is also a markedly increased risk for spina bifida. In animal studies, neural tube defects can result from both heat exposure and treatment with valproic acid. Mice resistant to heat-induced neural tube defects failed to produce offspring with neural tube defects when exposed to valproic acid, while strains with increased heat susceptibility demonstrated an increased frequency of neural tube defects when exposed to valproic acid (48).

TERATOGENS REQUIRE A CRITICAL TIME PERIOD FOR EXPOSURE In the human fetus most organogenesis takes place between days 18 and 60, with

exposure to a teratogen during this time having the greatest likelihood of resulting in a structural abnormality. Within this time period the various organ systems form at unique times and rates. For a drug to produce a teratogenic effect within a specific organ system, the fetus must be exposed to the drug while the organ is forming. This is termed the critical period.

Prior to the period of organogenesis, from fertilization to embryonic differentiation, the embryo consists of pluripotent cells. Exposure during this time results in either embryonic death or survival with no effect. After the period of organogenesis, the remainder of pregnancy involves growth and functional maturation of the already formed organ systems. Fetotoxic drug exposure at this time may result in functional disabilities and alterations in fetal growth.

Thalidomide The thalidomide embryopathy clearly illustrates the importance of a critical period in determining the production of an agent-specific syndrome. In a retrospective analysis of the available data, Lenz (9) reported that the time during which the fetus was most sensitive to the teratogenic effects of thalidomide was between days 34 and 50, using the first day of the last menstrual period as a reference point. Even within this time, specific effects generally occurred with exposure on specific days, defining the critical time period for the different anomalies seen with thalidomide embryopathy (5, 9). With exposure between the 34th and 39th days only the ears and cranial nerves were affected. Limb reduction defects occurred with exposure shortly after this. Embryonic exposure on the 39th to 43rd day resulted in reductions in armlength while exposure between the 42nd to 46th day was associated with reductions in lower extremity length. Only digital malformations were present with exposure between the 47th and 50th days.

Isotretinoin Isotretinoin is a more contemporary example, demonstrating that even limited exposure during the critical time period may result in profound structural malformations of the central nervous system, ears, and cardiovascular system. Based on current epidemiologic data, Rosa et al (49) identified the period of greatest sensitivity to isotretinoin to be between the second and fifth weeks postconception. Brief exposures, from three to eight days duration, during this time period have resulted in the full constellation of malformations typically seen with isotretinoin exposure (50–52). However, unlike thalidomide, this cluster of anomalies is present regardless of the time of exposure within the critical time (49).

MECHANISMS OF ACTION Another proposed property for a teratogen is that it must exert its cellular effects through a specific mechanism of action. These cellular effects, in turn, must result in the abnormal development of the

specific organ systems typically involved in the clinical malformation syndrome without damaging other organ systems that may be developing at the same time.

Wilson (26) has suggested nine potential mechanisms of action for teratogens (Table 6). Some, but not all, of these mechanisms have been demonstrated experimentally. Elucidation of other teratogenic mechanisms awaits the identification of the proximate toxin in some cases and the molecular target(s) in others.

Folate antagonism Folate antagonism decreases the availability of substrates needed for nucleic acid biosynthesis. Interference with folate metabolism and ultimately nucleic acid synthesis has been suggested as the mechanism responsible for the developmental toxicity of phenytoin and the folate antagonists, methotrexate and aminopterin.

Maternal folate levels are reported to decrease throughout pregnancy and this decrease is augmented in patients on anticonvulsant therapy (53). Some investigators have argued that similarities exist between the fetal aminopterin and fetal hydantoin syndromes, especially with respect to minor anomalies of the face (54). However, fetal exposure to phenytoin would be expected to occur throughout pregnancy and therefore all organ systems should be affected by the resultant inhibition of nucleic acid synthesis. Moreover, the two syndromes have different clinical expressions with the hydantoin syndrome uniformly involving digital anomalies while the aminopterin syndrome is characterized by cranial dysostosis, hydrocephalus, and anomalies of the external ears (38, 55).

Mitotic interference Another proposed mechanism for phenytoin embryotoxicity may be related to mitotic interference early in embryonic development. Estus & Blumer (56) demonstrated, using a sea urchin embryo model, that brief exposures to phenytoin during the M phase prior to the first cleavage resulted in asymmetric, incomplete, and arrested cleavage. It was

Table 6 Cellular mechanisms of action for teratogens (26)

Mutation
Chromosomal nondisjunction and breaks
Mitotic interference
Altered nucleic acid integrity or function
Lack of precursors and substrates needed for biosynthesis
Osmolar imbalance
Altered membrane characteristics
Altered energy sources
Enzyme inhibitions

proposed that interference with the mitotic spindle could be responsible for these malformations. Subsequent studies in the same model system demonstrated that exposure to phenytoin during this critical stage of development resulted in inhibition of microtubule assembly (57).

FETAL INJURY While this review is focused on fetal malformations, other abnormal outcomes can result from exposure to embryo- and fetotoxic agents. These would include growth retardation, functional disability, and fetal demise. Table 7 includes some agents possibly associated with these complications. With prolonged exposure to a teratogen, more than one of these complications can result. For example, the fetal alcohol syndrome consists of typical facial anomalies, intrauterine growth retardation, and mental deficiency (75). While the facial abnormalities may be the result of exposure at a specific period during development, the other aspects of this syndrome may be the result of exposure throughout gestation.

PHARMACOKINETICS AND EMBRYOTOXICITY The pharmacokinetic profile of a drug may influence its apparent teratogenicity in that pharmacokinetics largely determines the extent of fetal drug exposure. The latter is determined largely by the function of the maternal-placental-fetal system. Maternal drug absorption, distribution, and elimination all influence the availability of the drug for fetal exposure. Although the placenta separates the maternal and fetal compartments it rarely prevents fetal exposure as essentially all drugs are capable of crossing this structure. The rate and extent to which these compounds cross the placenta are determined by their physicochemical characteristics (76). These would include the drug's lipid solubility, polarity, and molecular weight.

Since most drugs are expected to cross the placenta to some degree, Levy (77) has concluded that maternal-fetal concentration gradients result from the presence of either a "shallow" or "deep" compartment in either the mother or

Table 7 Drugs associated with fetal injury

Growth retardation	Fetal death	Functional disorder
Aspirin (58, 59)	Aspirin (58, 59)	Antidepressants (71)
Caffeine (60)	Cocaine (61)	Benzodiazepines (72)
Cocaine (61, 62)	Narcotics (65)	Carbamazepine (36)
Marijuana (63)	Nicotine (67)	Methadone (73)
Narcotics (64, 65)	Propanolol (69)	Nicotine (74)
Nicotine (66, 67)		
Propanolol (68, 69)		
Steroids (70)		
Thiazides (69)		

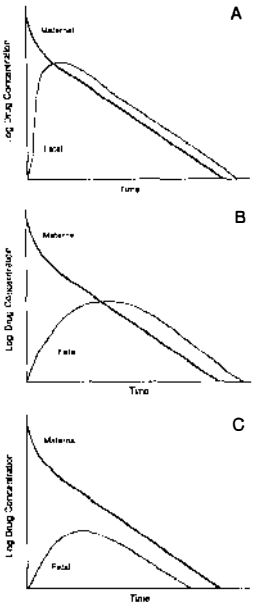

Figure 1 Examples of maternal-fetal pharmacokinetics demonstrating: (A) rapid distribution of the drug to the fetus without accumulation; (B) accumulation of the drug within the fetal compartment secondary to either a Ph or protein binding gradient; and (C) decreased transfer of the drug to the fetus due to a greater affinity in the maternal compartment.

the fetus. A shallow compartment is characterized by rapid delivery and distribution of a drug, while a deep compartment reflects slow drug delivery or a preferential gradient to the mother or the fetus. Waddell & Marlowe (78) have described the three most commonly seen scenarios in maternal-fetal pharmacokinetics (Figure 1). Substances that cross the placenta easily are rapidly distributed, and are not subject to a protein binding or pH gradient would demonstrate the kinetic profile shown in Figure 1.A. In this setting, the fetal drug concentration is most dependent on the maternal drug concentration and a shallow fetal compartment exists due to the absence of fetal drug accumulation. Figure 1.B demonstrates a deep fetal compartment with delay in the peak concentration of the drug in the fetus after maternal exposure. This is the result of either more extensive fetal protein binding or ion trapping in the fetal compartment producing a pH gradient into the fetus. Delayed peak concentrations associated with decreased area under the fetal concentration versus time curve may result when a drug has greater affinity for maternal than fetal compartment components (Figure 1.C). This may result from preferential protein binding in the maternal compartment or a pH gradient towards the mother. It could also be due to fetal or placental metabolism or to distribution into a very large fetal compartment.

Drug distribution within the fetus is clearly an important factor determining the degree of fetal exposure and is largely regulated by variations in pH and protein binding. In early pregnancy, the intracellular pH in the fetus is higher

than in the mother, resulting in the sequestration of weak acids and the potential accumulation of acidic drugs within the fetal tissues. Nau & Scott (79) demonstrated that valproic acid, a weak acid, accumulated in the mouse embryo whereas valproamide, the neutral amide congener of valproic acid, did not accumulate. As gestational age advances, the fetal intracellular pH becomes more acidic, resulting in the potential for the ion trapping of weak bases such as verapamil, a drug used to treat fetal tachycardias.

Variations in fetal protein binding also occur throughout pregnancy (80). The serum concentration of alpha 1-acid glycoprotein, which binds basic lipophilic drugs, is decreased in the fetus as compared to the mother throughout pregnancy, being negligible at 16 weeks gestation and one third of maternal concentrations at delivery. Albumin, which binds acidic lipophilic drugs, is present in the 12 to 15 week fetus although maternal concentrations are 3 to 4 times greater than fetal levels. However, as gestational age advances, the fetal concentrations of albumin increase as compared to the mother and at term are approximately 20% greater than the maternal concentration.

In general, acidic drugs would be more highly protein bound in the fetus and experience ion trapping; therefore, they would be described as having a deep compartment. In contrast, basic drugs, early in pregnancy, would demonstrate both a pH and protein-binding gradient towards the mother and, therefore, have a shallow compartment, exhibiting the pharmacokinetic pattern shown in Figure 1.C.

Drug metabolism within the fetus has been demonstrated as early as six weeks of gestation (81, 82), however the degree to which this influences teratogenicity is unclear. While most xenobiotic metabolizing systems in the fetus demonstrate less activity than those found in the mother, certain isoenzymes may actually be more active. 5-HT undergoes conjugation more rapidly in the fetus than in adults (82).

Reactive intermediates have been proposed as the proximate teratogens for several agents. Electrophilic arene oxides have been suggested as possible mediators of the embryotoxicity of phenytoin (43, 83). Much of the data supporting these arene oxides as proximate teratogens is indirect as these compounds have not been isolated. It is also unclear whether the embryo is capable of producing these reactive intermediates during the critical period for developmental toxicity. Some have argued that they may be produced in the mother and transported to the embryo (83); however, such electrophilic intermediates are unlikely to cross the placenta in quantities sufficient to cause significant developmental aberrations.

TERATOGENIC POTENTIAL IS DOSE-DEPENDENT One of the essential characteristics of a teratogen is that its effects must be dose-dependent. Increasing the dose should result in increased toxicity, from no fetal effects to lethal

effects. The dose-dependency of the embryotoxic effects may be an important difference between teratogenesis and carcinogenesis and mutagenesis. In the latter, structural abnormalities result from the alteration of a single cell from which other cells are derived. Therefore, any dose capable of affecting a single cell can result in carcinogenesis or mutagenesis. However, for a fetal malformation to be expressed a critical number of cells must be injured and/or cellular regeneration must be impaired, indicating that a dose-effect threshold exists.

Furthermore, a teratogen must produce its embryotoxic effects within a dosing range that is not toxic to the mother. As pointed out by Karnofsky (84), fetal malformation can result from exposure to any agent if large enough doses are used. To demonstrate abnormal embryogenesis following exposure to unusually high doses which would not be tolerated by the mother, does not indicate that the agent is a teratogen.

Ethanol It is frequently argued that any ethanol use during pregnancy can result in the fetal alcohol syndrome. However, a dose-response relationship has been described for fetal ethanol exposure. Brown et al (85) cultured rat embryos in either 150 or 300 mg/dl of ethanol from gestational days 10 through 12 and demonstrated a significant increase in growth retardation with the increasing dose. No fetal malformations were noted; however, the experiments were conducted at a time beyond the critical time for malformation, which is between 7 and 10 days of gestation (86, 87). Sulik et al (86) found that embryos developed typical craniofacial anomalies and growth deficiencies when mice were injected with two doses of 3 grams/kg (total of 6 grams/kg) ethanol on the seventh day of gestation, achieving blood concentrations of 200 mg/dl. Blakley & Scott (87) administered a single dose of ethanol on day 10 of gestation and demonstrated that the dose threshold for growth retardation was 4 grams/kg and for malformations was between 4 and 6 grams/kg. The highest dose tested, 7 grams/kg, resulted in fetal wastage of 50%.

In humans, Ouellette et al (88) found differences in the severity of malformations between rare, moderate, and heavy (greater than 45 ml of absolute alcohol per day) drinkers. Minor anomalies increased from 5% in rare drinkers to 12% and 15% in moderate and heavy drinkers, while major anomalies were 2 to 3% in rare and moderate drinkers and 17% in heavy drinkers. Ernhart et al (89) found a dosing threshold for all abnormalities, both the typical craniofacial anomalies and other major malformations, at 90 ml absolute alcohol/day. Little et al (90) demonstrated that occasional consumption (10 grams/day or 13 ml/day) resulted in a decrease in the infant birth weight by 225 grams. There was no mention of the presence of congenital malformations.

Therefore, both animal and human studies have indicated that a graded

dose-response relationship for craniofacial malformations and growth retardation exists in the fetus exposed to ethanol. It appears that low doses may result in growth retardation while higher doses result in increasing risk for malformations and fetal demise.

FETAL PHARMACOTHERAPY

Pharmacotherapeutic management of the compromised fetus is steadily gaining popularity and may ultimately prove an indispensable aspect of obstetrical care. Successes in transfusion therapy for the prenatal management of fetal hydrops secondary to Rh isoimmunization have generated interest in developing other antenatal therapeutic modalities (91). Also, improved methods for fetal evaluation have made possible early prenatal diagnosis and improved fetal monitoring during therapy.

Several aspects of fetal therapy warrant further investigation. In some cases, a more complete understanding of the pathophysiology of fetal disease is required in order to clarify the need for intervention. For example, the incidence of fetal tachyarrhythmias and the subsequent risk of fetal hydrops is still undefined. Thus the routine treatment of these rhythm disturbances in utero may be a questionable practice. Furthermore, prenatal treatment may be more difficult than postnatal treatment. Fetal therapy frequently involves drug administration to the mother, potentiating the risk of maternal toxicity. The latter, in turn, may further jeopardize an already compromised fetus. As the fetal patient is not as accessible to monitoring as the postnatal patient, inadvertent fetal toxicity or insufficient therapy, may occur and continue unrecognized. Therefore, a careful assessment of the risks and potential benefits must be considered prior to the initiation of fetal pharmacotherapy.

The three diseases in which fetal pharmacotherapy has been studied most extensively have been fetal toxoplasmosis, masculinization secondary to 21-hydroxylase deficiency, and fetal tachyarrythmias. However, even within these contexts, there have been no well-controlled studies documenting the safety and efficacy of therapy.

Fetal Toxoplasmosis

Acute infection during pregnancy with *Toxoplasma gondii* can result in fetal infection which is associated with severe neurologic and ophthalmologic diseases. Therefore, the infected mother had to choose between termination of the pregnancy or delivery of a potentially devastated child. Recent studies suggest that maternal and fetal therapy appear to significantly improve the outcome of these pregnancies (92, 93).

Toxoplasma gondii is a parasite capable of crossing the placenta and infecting the fetus at any time during pregnancy. The time of fetal exposure

appears to be the major determinant of outcome (94). When the mother is infected between the second and sixth months of pregnancy, there is an increased rate of neurologic disease in live-born offspring, with associated hydrocephalus and areas of cerebral necrosis; infections occurring later in pregnancy also can result in an infected offspring, but some, initially, may have no overt signs of disease. Nevertheless, these children remain at risk, particularly for the later development of ophthalmologic disease (94).

Two approaches to fetal therapy have been investigated depending on the presence of a documented fetal infection. The diagnosis of a fetal infection is made by serologic testing of the fetal blood or isolation of the parasite from either the fetal blood or the amniotic fluid. In the infected mother, but noninfected fetus, treatment with spiramycin is begun. This drug appears to concentrate in the placenta, thus potentially protecting the fetus from infection (95). It has been demonstrated that the number of negative placental cultures increased from 11% to 25% with spiramycin treatment (96). Further protection of the fetus may be afforded by the use of pyrimethamine and either sulfadiazine or sulfadoxine in addition to spiramycin as this combination results in an increase of negative placental cultures to 50% (96).

The therapy and outcome is different among infected fetuses. In this situation, 34 of 89 pregnancies were terminated because ultrasonography demonstrated severe cerebral damage (93). Of the remaining pregnancies, 37 received pyrimethamine, sulfadiazine, and spiramycin, 6 received sulfadoxine and pyrimethamine while 9 received spiramycin alone (92, 93). While these studies were not controlled, when the outcomes in these patients were compared to a previous study of untreated patients there appeared to be significant improvement in outcome. Severe damage decreased from 10% to 2% while offspring with no neurologic or ophthalmologic disease increased from 54% to 76% (93). No differences in the outcomes or infants receiving different therapies was discussed.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), an autosomal recessive disorder, is the result of inadequate cortisol synthesis secondary to a deficiency of fetal 21-hydroxylase. In the classic homozygous form of the disease, increased secretion of ACTH, and the resulting androgen excess, results in virilization of the external genitalia. The advantage of prenatal therapy would be the prevention of this virilization thereby avoiding the need for surgical correction after birth.

It is now possible to diagnose CAH in the first trimester of pregnancy using HLA typing or DNA analysis (97). This represents an important advance in prenatal diagnosis since effective therapy must begin by at least the seventh week of gestation in order to prevent virilization. Evans et al (98) attempted to

treat CAH in the fetus and demonstrated that the administration of dexamethasone to the mother resulted in suppression of the fetal adrenal gland function. Although the patient in this study was later found not to have CAH, in theory, fetal adrenal gland suppression is possible and could result in the prevention of virilization of the affected females.

Clinical results in the prenatal treatment of CAH have been variable. The therapeutic outcomes of fourteen female infants with CAH treated prenatally with either dexamethasone or hydrocortisone were reviewed recently by Pang et al (97). Five newborns had normal female genitalia, five demonstrated partial virilization and four demonstrated marked virilization. While the authors suggest endocrinologic reasons for the failure seen with steroid therapy, the pharmacologic basis for their results is also discussed.

In some of the treatment failures, it is apparent that suppression of the fetal adrenal was inadequate. This was demonstrated by David & Forest (99) in one patient treated with hydrocortisone in which the amniotic fluid contained high levels of 17-hydroxyprogesterone, androstenedione, and testosterone. These authors postulated that dexamethasone may be preferable to hydrocortisone since the latter is bound more extensively by transcortin, resulting in less free drug for placental transfer (99, 100). However, since the amount of free drug should be equivalent in both the maternal and fetal compartments with prolonged use, adequate fetal drug concentrations should be achieved. Another possible explanation for the apparent therapeutic superiority of dexamethasone, is that this longer-acting glucocorticoid produces a more physiologic glucocorticoid effect with more consistent ACTH suppression (101).

Possible explanations for the four treatment failures managed with dexamethasone is that the initiation of therapy was delayed beyond the tenth week of gestation or that therapy was interrupted prior to delivery (100). There also appears to be interindividual variation in the degree of adrenal suppression achieved on the same dose of dexamethasone (102, 103). Therefore, recommendations to determine the degree of fetal adrenal suppression by measuring 17-hydroxyprogesterone and androgens in the amniotic fluid seem prudent (97).

Although it would appear that more experience with this therapeutic approach is needed to define further dosing regimens and maternal and fetal complications, the preliminary data would suggest that prenatal treatment of CAH is feasible.

Fetal Tachycardia

Fetal arrhythmias can be divided into either irregular rhythms, rapid rhythms, or bradycardias. These occur in approximately 1% of all fetuses with only 10% of these arrhythmias capable of increasing fetal mortality and morbidity

(104). The tachycardias, usually supraventricular, create the greatest concern because, if sustained, they may be associated with congestive heart failure as evidenced by hydrops fetalis. Despite this concern, controversy remains concerning the appropriate management of these rhythm disturbances in utero.

One concern is the appropriateness of treating a nonhydropic fetus with supraventricular tachycardia (SVT) as the natural course of fetal SVT is unclear. Kleinman et al (105) found 15 of 16 fetuses with SVT were also hydropic on initial examination. However, Bergman et al (106) in a review of the literature found only 22 of 45 fetuses with SVT to be hydropic. This is consistent with the experience of Maxwell et al (107) who found 7 of 15 fetuses with SVT to be hydropic at the time of diagnosis. Therefore, it is apparent that not all fetuses with SVT will develop hydrops, suggesting that aggressive therapy of the non-hydropic fetus may not be warranted.

Another point of controversy is whether a hydropic fetus would be better managed prenatally or postnatally; that is, should fetal pharmacotherapy be instituted or should the fetus be delivered (108, 109). Clearly the only treatment modality for the hydropic fetus at a nonviable gestational age would be in utero therapy, but many others are diagnosed at a time when they would be viable. Therefore, in these latter infants, there must be clear benefits to in utero management. Although numerous brief reports exist on the prenatal management of SVT, to date, there have been no controlled studies attempting to define the safety and efficacy of this approach.

As in SVT in adults, digoxin has been considered the drug of choice (104, 105). In the normal fetus, this drug appears to cross the placenta easily, achieving levels of unchanged digoxin similar to those found in the mother within 30 minutes (110). Unfortunately, most reports do not take into account the variable presence of digoxinlike immunoreactive substance with the result that most data demonstrating adequate maternal or fetal concentrations should be viewed cautiously.

Furthermore, there is evidence that the pharmacokinetics of digoxin are altered in the compromised fetus. Placental transfer of digoxin to the hydropic fetus appears to be markedly reduced (111, 112). There is only one report of the fetal pharmacokinetics of digoxin in a hydropic fetus. Weiner & Thompson (111) injected digoxin directly into the fetal muscle and using two fetal drug concentrations estimated that the fetal volume of distribution was 97 L/kg and the half-life was 15.9 hours. These are remarkably different from the usual neonatal values of 12 to 16 L/kg and one to four days (113). This would indicate that the fetal clearance is increased largely as a function of an increased volume of distribution and suggests that very large doses would be required to achieve suggested therapeutic drug concentrations. Therefore, whether digoxin in sufficient quantities to treat the arrhythmias has been

present in any of the fetuses who have been reported to respond is questionable.

Nevertheless, there are numerous case reports of fetal SVT resolving with digoxin therapy (107, 114, 115). Of interest in these studies is the prolonged period of time needed to control the arrhythmia in the fetus with or without hydrops. From the cases of SVT reported in which the time to response is stated, only four of 16 responded in less than three days, while nine required therapy for more than seven days and four for more than 21 days. One fetus was treated for 42 days before control was achieved (107). Whether these delayed responses are due to the slow accumulation of digoxin in the fetus or the natural resolution of the SVT in the patient cannot be determined.

When initial therapy with digoxin is unsuccessful, other agents have been added. The most commonly used second agents are either verapamil or procainamide. Both of these agents may actually accumulate in the fetus as they are weak bases (114). The scattered case reports again make it difficult to evaluate the efficacy of these two agents. Amiodarone has also been used but infrequently. Very little is known of the fetal pharmacokinetics of this drug. Quinidine was reported in one study to stabilize SVT in patients refractory to digoxin (116). However, this treatment success could be due to increased digoxin levels as was reported in two of the three patients.

The possible complications of the use of these agents prenatally should also be weighed against therapeutic gain, especially in nonhydropic patients. Owen et al (117) report a case of fetal demise after resolution of SVT and hydrops in which both digoxin and verapamil were being used. Drug accumulation of digoxin with the concomitant use of verapamil or synergistic effects on the AV node were considered to contribute to fetal death. Amiodarone contains a large amount of iodine, 75 mg in a 200 mg dose, which is known to cross the placenta and concentrate in the fetal thyroid tissue (114). Abnormal thyroid function tests were demonstrated in a neonate treated with amiodarone antenatally (118). Therefore it would seem wise to use this drug with caution.

While there is increasing evidence that a certain number of fetuses with SVT will require therapy, further delineation of the criteria for initiating therapy is required.

CONCLUSION

This review has attempted to describe the two areas of most active research regarding fetal drug exposure, namely teratology and fetal pharmacotherapy. While many agents have been implicated as resulting in adverse side effects, only a limited number have been studied adequately. This is a particularly disturbing finding as we begin more aggressive fetal therapy. Therefore, more

carefully designed studies are needed, with particular emphasis on attaining a clearer understanding of fetal pharmacokinetics and pharmacodynamics in order to adequately assess teratologic or therapeutic potential.

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