Congenital Malformations with Psychopharmacologic Agents

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PSYCHOPHARMACOLOGICAL AGENTS are frequently used and often for a long time because of the chronicity of mental illness. Ayd reports that about 250 million people have taken these drugs.[3] This number probably includes a considerable number of pregnant women. The safety of psychotropic drugs for the fetus has not been established with certainty, even though none except thalidomide is incriminated. The conclusive evidence can only be obtained by monitoring of fetal effects. In this paper, the fetal effects, particularly teratogenesis, of the psychopharmacologic agents are reviewed.

PHENOTHIAZINES

In December 1962, the Canadian Food and Drug Directorate issued a statement that the administration of trifluoperazine was noted to have been associated with eight cases of congenital malformations manifesting in skeletal, as well as multiple internal deformities.[8] The reported congenital anomalies included hydrocele, hydrocephaly, polydactyly, and clubbed feet, with mongoloid features in five live infants.[38] Corner[10] reported skeletal abnormality in a pair of twins whose mother had received trifluoperazine during the first 6 months of pregnancy. Vince[60] reported the occurrence of complete transposition of great vessels with patent foramen ovale in a baby born to a 34-year-old woman with one previous normal pregnancy who received thioridazine, 25 mg daily for 3 months before conception and for the first 5.5 months of pregnancy. She also received 4 mg of trifluoperazine daily for the first 4 months of pregnancy. In addition, a baby with hydrocephalus, meningomyelocele, and hypospadias born to a mother who received thiethylperazine from the ninth to thirteenth weeks of pregnancy has been reported.[43] Similarly, congenital malformation in infants born of mothers who received prochlorperazine[17] has been documented. A 20-year-old nullipara who received 50 mg meclizine starting from the fifth week and chlorpromazine 50 mg daily starting from the sixth week of pregnancy, both of which were continued until termination, was delivered of a 1-lb 13-oz stillborn fetus with a large omphalocele that had ruptured with extrusion of its intraabdominal contents, along with complete absence of one lower extremity.[46]

On the other hand, Favre-Tissot and Brousolle[16] studied babies of three groups of mothers. The first group of 17 mothers who received phenothiazines before pregnancy delivered 1 premature and 16 full-term infants. Of the 16, 1 had craniostenosis. The second group of 316 women, who received phenothiazines before the third month of pregnancy, delivered 310 full-term infants including 2 sets of twins and 1 set of triplets. In addition, there were 8 abortions and 4 premature

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births. Among the live-born, there were 10 malformed infants (3.2%) 4 minor malformations (1 hydronephrosis and 3 club-foot), 4 cardiopathies (3 systolic murmur and 1 mitral insufficiency, patent ductus, and genu valgum), and 2 complex malformations (cleft palate, platycephaly, syndactyly, and absence of nails). The third group of 62 women, who received phenothiazines after the third month of pregnancy, delivered 52 infants born at the end of full term, of which 1 was malformed. Two women had prolonged gestation, and 2 deaths of infants occurred. Therefore, there is no appreciable difference between the three groups.

Similarly, Kris[23] did not find any congenital defects in the babies of 14 mothers who received chlorpromazine 50 to 150 mg daily throughout pregnancy. Follow-up of these children up to a 4-year period did not reveal any abnormalities.[23,24] Sobel[55] studied 52 women treated during pregnancy with chlorpromazine and reported four cases of fetal damage in mothers receiving large doses. He concluded, however, that the overall incidence of fetal mortality and morbidity was not increased. The incidence of fetal damage in his group was 8%, almost identical with the 7% in the control group. In another study, chlorpromazine given orally or intramuscularly for nausea and vomiting in doses up to 150 mg daily produced no harmful effects on the mother or the child.[5]

The reported isolated malformations also need scrutiny. Schire,[52] on further analysis, found that, among the eight cases of congenital deformities reported where the mothers were said to have taken trifluoperazine, two aborted between the third and fourth months of pregnancy. Both of them had also received cyclical hormone therapy up to the time of conception and an antiemetic preparation subsequently. In two others, there was a history of other drug intake and one of these two had a family history of congenital defects. The fifth patient received a variety of psychotropic medication for the treatment of psychiatric illness. In the other three, information was still not available. Therefore, incriminating trifluoperazine in any of these cases seems far fetched. Moriarity and Nance[39] compared the incidence of congenital malformations in 480 trifluoperazine-treated patients with 8472 in a control group. The incidence of congenital malformations in the trifluoperazine-treated and the baseline groups were 1.1% and 1.5%, respectively. This study revealed no evidence of a causal relation between the administration of trifluoperazine and the production of congenital malformations.

Therefore, one can assume that controlled studies have proved that the phenothiazines can safely be administered to pregnant women without the danger of teratogenic effects, and isolated reports do not provide enough evidence for incriminating the phenothiazines. More important is that, in spite of use by millions, the almost total absence of teratogenicity of phenothiazines is conspicuous.

ANTIDEPRESSANTS

The New Zealand Committee on Adverse Drug Reactions[43] reported over a 2-year period, cases of congenital anomalies associated with the administration of antidepressant medication to pregnant women and also reported a baby with spina bifida occulta born to a woman who received protriptyline and diazepam for the first 4 months of pregnancy. McBride[31] reported three children born with

limb deformities whose mothers had ingested imipramine or amitriptyline during the first trimester of pregnancy. Robson and Sullivan[50] found imipramine to be teratogenic in rabbits. However, an extensive review of the data on the mothers who delivered babies with similar deformities was undertaken[49] to verify these findings. Among the 196,784 births, reduction deformity was noted in 120 babies. Interview of many mothers of this group confirmed that none of the interviewed had taken antidepressant medication. In another survey,[4] 168 cases of reduction deformities were noted. In 143 out of the 168 cases, the maternal history during the first 12 months excluded the use of tricyclic antidepressants. In two cases, an unknown tranquilizer was stated to have been taken. One mother had used amitriptyline during the first 12 weeks of her pregnancy, and the infant had absent digits and hydrocephalus. IdanPaan-Heikkila and Saxen[20] reviewed 2784 cases of birth defects taken from the Finnish register of congenital malformations for 1964–1972 and an equal number of matched controls to discover which mothers had used tricyclic antidepressants during pregnancy. Combined use of an imipramine and chloropyramine in the first trimester was associated with the occurrence of two craniofacial malformations and central nervous system anomaly in the infants. Three more infants with malformations were born of mothers who received amitriptyline during pregnancy. These findings do not provide enough evidence for the teratogenicity of the tricyclic antidepressants.

LITHIUM

Isolated cases of congenital anomalies in the mothers who had received lithium during pregnancy have been reported by Aoki and Reudy,[1] Lewis and Suris,[27] and Vacaflor, Lehmann, and Ban.[59] To resolve the controversy of the safety of lithium in pregnant women, Schou et al.[53] analyzed reports contained in the register of lithium babies. Out of the 118 children reported, five were stillborn, and seven died within the first week of life. Six of these 12 children were malformed. In addition, there were three more malformed surviving children, making the total nine. Of the nine cases, the cardiovascular system was involved in six cases. Therefore they concluded that the risk of teratogenic effects of lithium was not found to be significant.

Among the reported cases of malformations, one of the patients reported by Vacaflor, Lehmann, and Ban[59] and Aoki and Reudy[1] is the same. This woman had received chlorpromazine, metronidazole, and bendroflumethiazide during pregnancy. In addition to the medications, she had developed early signs of toxemia of pregnancy as well as lithium intoxication during pregnancy. Therefore, the role of lithium alone is at best doubtful. Lewis and Suris[27] reported the occurrence of coarctation of aorta in the baby of a mother who had received lithium for the first 8 weeks of pregnancy. However, they do not provide either the patient's drug history or genetic history.

On the basis of the available evidence, lithium seems to be as safe as any other drug for pregnant women. The incidence of malformations noted by the lithium register does not seem to be higher than that in the general population. Moreover, it is difficult to incriminate lithium even in the reported cases of malformations in the babies born to mothers who had received lithium during pregnancy.

AMPHETAMINES

The literature is replete with instances of fetal malformation with the use of anorexiants. A mother took phenmetrazine from the fourth to twelfth weeks in two pregnancies and both times produced an infant with the left diaphragmatic defect and herniation of abdominal organs into the thoracic cavity. Her other four children and a still birth were free of malformations, and these pregnancies were unassociated with the ingestion of the drug as well.[48] Lenz[25] reported a similar malformation in an infant born to a woman who had taken 25 mg of phenmetrazine daily starting around the 19th day of pregnancy. Another report on phenmetrazine included an infant with deformities of one hand and lower limbs.[40] Three mothers of children born with transposition of the great vessels had taken dextroamphetamine sulfate during the early weeks of pregnancy in order to suppress appetite.[44] Two retarded children were born of a mother who received a combination of methamphetamine hydrochloride and phenobarbital starting at the end of the second month.[33]

Nora, McNamara, and Fraser,[45] conducted a retroprospective study of prenatal factors in 219 infants and children under 2 years with congenital heart disease (CHD). A thorough family history was obtained for each patient. They were compared with the pregnancy histories in a control group of 153 mothers with children with no CHD. Thirty-one and one-tenth per cent of the 210 probands and only 5.9% of the 153 control probands had a positive family history. This difference is highly significant ($p < 0.001$). The proportion of cases with both a family history and a history of maternal exposure to dextroamphetamine was that expected if these factors were independent of one another. Therefore, retrospective data did not provide any evidence for a causal association between exposure to dextroamphetamine sulfate during pregnancy and CHD. In a prospective study, 52 mothers who had a documented exposure to the drug during the vulnerable period of a cardiac development and their infants were later examined for CHD. The results were compared to those of 50 mothers not exposed to the drug. No significant difference was noted in the number of congenital malformations. Thus, even the prospective approach did not provide any evidence of a relation between maternal exposure to dextroamphetamine sulfate and the occurrence of CHD.

HYPNOTICS

Bromides

Bromides are easily obtainable without prescription. Opitz, Grosse, and Haneberg[47] reported that a young woman who had two normal children before, and another 5 years after, drug abuse gave birth to two boys manifesting growth retardation and small heads. One of these two boys was microcephalic and had congenital heart disease. During the two latter pregnancies, she was consuming large quantities of Bromo-Seltzer. A similar abnormality in another child born of a mother who was consuming bromides heavily during pregnancy has been reported.[51]

Glutethimide

Glutethimide is similar in chemical structure to thalidomide. However, the manufacturers claim that the avenues of breakdown differ considerably. Two

cases of children born with limb abnormalities of mothers who had received glutethimide during the second month of pregnancy have been described.[36] Cleven and Bartholemew, quoted in the above mentioned article, report the occurrences of peripheral neuritis in patients receiving this drug similar to that of thalidomide.

Thalidomide

Following McBride's[30] discovery that thalidomide causes certain types of skeletal and multiple malformations in humans, many such reports have followed. Excellent and critical reviews by Lenz[26] and Taussig[58] reveal the incidence and historical data. Thalidomide has been alleged to be responsible for birth deformities of 6000 babies, around 4000 of whom are from West Germany.[11] Teratogenicity of thalidomide is well established.

ANXIOLYTICS

Diazepam

Absence of both thumbs, including metacarpal bones, and dislocation of the head of the right radius were noted in a newborn female whose mother had been given diazepam, 6 mg daily for 3 weeks, starting a week after the last menstrual period, and hydroxyprogesterone over prolonged periods during pregnancy.[21] A case of spina bifida occulta in a newborn whose mother received diazepam and protriptyline for the first 4 months of pregnancy has been reported.[43] However, in both these instances, the mothers received drug combinations and thus do not provide evidence against the safe use of diazepam during pregnancy.

Antiepileptic Medications

The frequently used antiepileptic medications include phenobarbital and phenytoin. In addition to the fact that many epileptic patients manifest psychiatric problems, both these drugs are also used as psychopharmacologic agents to relieve anxiety. Six cases of congenital abnormalities in newborns whose mothers received phenobarbital (three) and phenytoin (three) were revealed in a survey.[42] Meadow[35] collected reports of 32 babies with cleft lip and cleft palate born to mothers on anticonvulsant therapy during pregnancy. Nineteen of these mothers were on phenytoin. This was more than twice the statistically predicted frequency of this deformity. Six of the 32 babies had minor skeletal abnormalities. Mirkin[37] found three fetal abnormalities in infants born of seven unselected mothers who received phenytoin. In a study of 17 neonates whose mothers received phenytoin, a case of diaphragmatic hernia and another with intrauterine retardation were revealed.[41] Seven infants with similar skeletal deformities, born of mothers taking phenytoin during pregnancy, have been reported.[28] The first large-scale survey was reported by Speidel and Meadow.[56] This retrospective survey into the outcome of 427 pregnancies in 186 epileptic women showed that major congenital malformations occurred in their children with twice the expected frequency. They had received antiepileptic medication, most often phenytoin and phenobarbital. By comparing 186 epileptic and 100 normal women, mental subnormality occurred in 1.5% of the epileptic mothers' children compared with 0.2% in the control group. Spellacy[57] found three congenital anomalies (5.8%) in 51 treated epileptic patients and none in 50 matched controls, indicating that epilepsy by itself is not responsible for the increased incidence of

congenital malformations. A survey of congenital malformations in infants born of mothers in Cardiff over a 7-year period revealed a malformation rate of 2.7%. Where the mother had a history of epilepsy and had been on anticonvulsant drugs during the first trimester, the rate was 6.7%.[29] McMullin[34] reported the occurrence of ambiguous external genitalia, large clitoris with other multiple malformations, in a live infant of a mother who received phenobarbital, primidome, diphenylhydantoin, phensuximide, and carbamezepine for epilepsy.

The fact that epileptic mothers have an increased chance of a baby with a major malformation should not prevent the action of most women with epilepsy or of their doctors in therapeutic situations. However, the evidence at hand calls for closer scrutiny and need for further work.

OTHER DRUGS

Disulfiram

Five pregnant women on disulfiram during the first trimester of pregnancy gave birth to two normal infants and two infants with clubfoot. The other ended in a spontaneous abortion.[16]

Alcohol

Eight unrelated children of three different ethnic groups, all born to mothers who were chronic alcoholics, have a similar pattern of craniofascial, limb, and cardiovascular defects.[22] As alcoholism is a major problem affecting many, a large scale prospective study is in order.

Lysergic Acid Diethylamide (LSD)

In three studies,[9,14,61] ingestion of LSD by pregnant women was shown to result in elevated numbers of chromosome breaks in their babies. Such chromosomal defects tended to repair incompletely.[7] These abnormalities may be the effects of drug abuse in general rather than to the effects of pure LSD.[12] McGlothlin, Sparkes, and Arnold[32] reported that frequencies of premature births and birth defects in 148 pregnancies in which one or both parents used LSD were similar to those of the general population.

There are a few reports of congenital malformations consequent to use of LSD during pregnancy. Zellweger et al.[62] reported the birth of a baby with a malformed right leg to a woman who used LSD during the first trimester. Hecht et al.[18] reported the birth of an infant with a malformed arm to a woman who used LSD, cannabis, and several antiemetic drugs. Carakushansky et al. (1969) reported the birth of an infant with a terminal transverse deficit of portions of fingers of the left hand and syndactyly of the right hand to a woman who used LSD and cannabis during pregnancy. Assemany, Neu, and Gardner[2] reported the birth of an infant with amputation deformities of the third finger of the right hand and the third toe of the left foot to a woman who had taken LSD throughout pregnancy. Hsu, Strauss and Hirshhorn[19] reported the birth of an infant with trisomy-13 to parents who used LSD. They suggested that LSD could have damaged the germ cells prior to pregnancy. Such a possibility cannot be discounted. Eller and Morton[15] reported the birth of an infant with severe deformities to a woman who had received estrogen and medroxyprogesterone

during the first trimester and had ingested LSD later in pregnancy. Blanc et al.[6] reported the birth of six malformed infants to mothers using LSD. Malformation consisted of amniotic band syndrome in three and fibular aplasia, trisomy-13, and spondylothoracic dysplasia in one each. They suggested that LSD may produce predisposition to early rupture or separation of amniotic membranes.

In all of these cases, it is difficult to distinguish LSD effect from those of impurities. Those patients reported had consumed illicit LSD. However, no congenital deformity as a result of maternal ingestion of pure LSD has been reported.

CONCLUSION

This extensive review of congenital malformations in the infants of women who received psychopharmacologic agents during pregnancy reveals the occurrence of very few cases of congenital defects. Therefore, the present evidence does not preclude the benefit of psychopharmacologic agents to those unfortunate pregnant women with mental illness or epilepsy. Even though existing psychoactive drugs are relatively safe to the fetus, ever increasing numbers of new psychopharmacologic agents are flooding the market, the safety of which has not been assessed in humans. Therefore, prevention of episodes similar to the thalidomide tragedy, depends in part on the physicians.

The only two sure ways of reducing drug-induced malformations are decreasing the susceptibility of the fetus and preventing pregnant women from taking any medication. The former is not possible, and the latter not practical. Therefore, safety measures need to be implemented. At the present time, animal tests for teratogenicity are not directly applicable to man.[13,54] Hence, in spite of reported safety in animals, pregnant women should receive only justifiable prescriptions of drugs. Many pregnant women need and therefore do take psychopharmacologic agents. The results of such clinical human experimentation need to be harvested. For this purpose, careful monitoring, reporting, and recording are necessary. Such monitoring ensures safety by not incriminating any drug, but at least discriminates the spectrum of safe and unsafe drugs. Pooling of all this information provides data on a large sample, clues for further research, and rapid dissemination of information. Early detection of new malformations may be possible. However, it is likely that psychopharmacologic agents may be harmful to the susceptible fetus. Future research may very well lead us to clues about eliminating fetal susceptibility to drugs. Such possibilities have been tested by the administration of glutamine to thalidomide-treated, gravid animals with consequent decrease in the number of malformed fetuses. For the present, care in prescribing, careful observation, and central recording by a registry may help us in further progress.

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