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Benzodiazepines and Pregnancy

Vol 4#2 September 1995

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It is estimated that 30 to 40% of pregnant women are treated with medications for anxiety during their pregnancy (McElhatton, 1994). The medications used for this purpose are often benzodiazepines, one of the most widely prescribed classes of drugs in the world. Benzodiazepines are used as anxiolytics, anti-convulsants, muscle relaxants, and sedatives. In addition to treating anxiety during pregnancy, they may also be used during normal deliveries, caesarean sections, and to treat eclampsia and preeclampsia (McElhatton, 1994). Benzodiazepines may also be abused by those addicted to drugs.

While many new benzodiazepines have been introduced in recent years, few studies have been conducted concerning their use during human pregnancy. Most of the information on benzodiazepine use during pregnancy is based on diazepam. Although initial studies suggested an association between first trimester use of diazepam and specific congenital anomalies, more recent reports have not supported these claims. Substantial evidence exists demonstrating that newborns of mothers treated with benzodiazepines near term or during delivery show classic drug withdrawal symptoms. This issue of RISK||NEWSLETTER will review the use of benzodiazepines during pregnancy.

RISK OF CONGENITAL MALFORMATIONS

Beginning in 1975, concern was raised over an association between first trimester use of diazepam and oral clefts in newborns (Saxen, 1974; Aarskog, 1975). In a retrospective study of 278 malformed children, Safra and Oakley (1975) found that pregnant women taking diazepam had a relative risk of four for having an infant with cleft lip (with or without cleft palate). These results have been criticized because the study introduced a possible source of recall bias by using a questionnaire to determine maternal exposure to diazepam. In addition, the study did not control for multiple drug use.

Later studies (Rosenberg et al., 1983; Shiono and Mills, 1984) found that first trimester use of diazepam posed no increased risk for oral clefts. Included in these studies was that of Czeizel (1988) which analyzed data obtained from the Hungarian Congenital Malformation Register. Information was collected on benzodiazepine (diazepam, nitrazepam, and chlordiazepoxide) use in four different studies using four different methods (both retrospective and prospective). The studies included over 350 exposed pregnant women and there was no indication that the use of benzodiazepines alone or with other drugs was associated with an increase in facial clefts or any other specific birth defects.

The possible teratogenicity of benzodiazepines was raised again when Laegrid et al. (1989) reported eight infants with birth defects whose mothers had taken diazepam or oxazepam while pregnant. Most of the abnormalities involved either facial defects or neurological problems. This study was criticized because photographs of the affected children revealed a physical appearance similar to that seen in

Zellweger syndrome, an autosomal recessive condition. The blood samples from these women were analyzed for benzodiazepines only, so it was possible that the women were exposed to other drugs. It is also important to note that three of the mothers in the study denied using any drugs during pregnancy.

In order to address the issue of the potential teratogenicity of benzodiazepines in a systematic manner and to avoid the criticisms of earlier studies, Pastuszak et al., (in Schardein, 1995) conducted a prospective study of pregnancy outcome following first-trimester exposure. The subjects and controls consisted of women who were seen through the Motherisk Program in Toronto. Pregnancy outcomes of 137 women who sought counseling after first-trimester exposure to benzodiazepines were compared to 137 women who sought counseling after exposure to drugs that are known to be safe during pregnancy. The most commonly used benzodiazepines in this study were diazepam, lorazepam, and alprozolam. A trained interviewer obtained information on pregnancy outcome over the phone; pregnancy outcome reports were confirmed by a written report sent to the clinic by the child's physician. No statistical difference in the rates of major birth defects were observed between the two groups. There were no cases of cleft lip and/or palate, and in fact, only one infant in the benzodiazepine exposed group had a congenital anomaly.

RISK OF NEONATAL WITHDRAWAL

The occurrence of withdrawal symptoms in infants of mothers exposed to benzodiazepines during pregnancy has been well documented (Cree et al., 1973; Gillberg, 1977; Haram, 1977). Neonatal withdrawal was most likely to occur when mothers were taking chronic doses of benzodiazepines near term or during delivery. Symptoms included hypotonia, respiratory distress, impaired temperature regulation, hyperactivity, and irritability. Signs of withdrawal were present at birth or appeared weeks later and continued for long periods of time (Besunder and Blumer, in Schardein, 1995). Elimination of benzodiazepines in the infant is slow, and it is thought that increased blood concentrations along with an immature blood-brain barrier may make newborns more sensitive to the drugs than adults (Pastuszak, in Schardein 1995). In addition to diazepam, withdrawal symptoms have also been observed in the infants of women who took clobazam, chlordiazepoxide, and lorazepam during pregnancy (Devreker et al., 1987; Stirrat et al., 1974; McBride et al., 1979).

Besunder and Blumer (1995) recommend that treatment of withdrawal should be initiated if the symptoms are causing poor feeding and weight gain or interfering with normal caretaker interactions. Initially, diazepam should be administered intravenously until symptoms have been controlled for one week, at which time the daily dosage should be weaned over three to four weeks. Schneiderman (in Schardein 1995) also recommended that pregnant women taking chronic doses of benzodiazepines attempt to achieve abstinence by gradual reducing their daily dose over a six to eight week period. Diazepam can be substituted for some of the shorter-acting benzodiazepines during detoxification in order to stabilize fluctuating blood levels of the medications. If abstinence cannot be reached through either outpatient or inpatient regimens, pregnant women should be given the lowest possible dose of benzodiazepines.

NEUROBEHAVIORAL EFFECTS

It has not been established that prolonged exposure in utero results in neurobehavioral disturbances, as suggested in certain reports. Laegrid et al., (1992) described 17 children whose mothers had psychiatric illnesses and were taking benzodiazepines during pregnancy. Compared to infants of mentally healthy mothers, the benzodiazepine-exposed infants showed delayed gross motor development at 6 and 10 months, but normal development by 18 months. Fine motor functions were impaired at all study periods. However, all major developmental milestones were achieved at the appropriate ages. Effects on long-term development were not evaluated.

Bergman et al., (1992) examined benzodiazepine use during pregnancy in deliveries registered with

Medicaid between 1980 and 1983. Eighty women were identified who had been given 10 or more prescriptions for benzodiazepines and thus were assumed to be chronic users. Forty (50%) of these women were exposed throughout their entire pregnancy. In addition, 30% of the women reported drug dependence during pregnancy, 14% reported alcohol dependence, and over 50% had a chronic illness such as liver cirrhosis or hepatitis. Follow-up was obtained on 64 children and 14 were found to have some signs of developmental delay. However, given the medical and social history of their mothers, environmental factors cannot be ruled out as significant contributors to their failure to develop normally.

SUMMARY

Studies concerning the teratogenicity of benzodiazepines have produced conflicting results. Recent studies, however, have not provided substantive evidence that in utero exposure to benzodiazepines causes an increase in any specific malformation or pattern of malformations. Early studies that reported an association with adverse outcomes were criticized because of recall bias and possible multiple drug use.

Infants of mothers taking chronic doses of benzodiazepines near term are at risk for developing withdrawal symptoms postnatally. For this reason, women should discontinue use well before delivery. If abstinence is not possible, the lowest possible dose should be used and one of the shorter acting benzodiazepines should be considered (McElhatton, 1994).

Many women who are taking benzodiazepines may have psychiatric illnesses, epilepsy, or be dependent on other drugs or alcohol. Maternal illness or drug abuse is likely to create an environment that is not optimal for normal infant development, both prenatally and postnatally. Each of these conditions are risk factors during pregnancy and, therefore, it is difficult to discern negative clinical effects due specifically to benzodiazepines, especially in relation to neurobehavioral dysfunctioning.