Prenatal and Perinatal Effects of Psychotropic Drugs on Neuro-cognitive Development in the Fetus

Eduard Bercovici

Note: In the text of this paper, the term "mental retardation" has been used in the diagnostic sense and to correspond with terminology used by authors who have been cited.

Abstract

There has been an increased dependence on prescription drugs for psychological and mood disorders in the last few decades. Many women who take these drugs may become pregnant and not be aware of their possible adverse effects. Since thalidomide, a drug used to treat morning sickness in pregnancy, was found to be teratogenic, many drugs are being screened more stringently for possible teratogenic effects on the fetus. Although newer drugs do not appear to cause congenital malformations, some still pose a threat. This review is aimed at summarizing the teratogenic effects of commonly used antiepileptics, antidepressants and anxiolytics. The effects of these drugs on intellectual and developmental disabilities or cognitive development have not been extensively studied. It is hypothesized that these drugs can alter development via two pathways. First, prenatal effects on neurotransmitters can alter brain circuitry, thereby predisposing children to later learning and behavioural deficits. Second, perinatal events caused by drug withdrawal upon delivery of the baby, may have long lasting effects on cognitive developments, as suggested by numerous animal and human studies. Various motor and respiratory side effects resulting in especially low Apgar scores may have deleterious consequences. Psychotropic drugs should be avoided during pregnancy unless deemed absolutely necessary for the benefits of both the mother and fetus. If drugs must be utilized, strict guidelines should be set to ensure that fetal withdrawal or dependency from these drugs does not occur. Finally, perinatal events should be meticulously noted for future reference during the development of the child.

Of the many factors that contribute to the occurrence of intellectual and developmental disabilities, it has been estimated that 15 - 29% may be attributed to teratogens.

One drug with devastating teratogenic effects is thalidomide. This was first prescribed in the late 1950s in Europe to treat morning sickness in pregnant women, as well as anxiety and insomnia generally. It was withdrawn from the market in the early 1960s when found to cause devastating birth defects, including major malformations such as missing arms and legs. Interestingly, thalidomide recently has been found to be an effective drug in the treatment of multiple myeloma (Hussein, 2005). Unfortunately, many of the current generation of young women of child-bearing age are not aware of the original thalidomide catastrophe. Consequently, they may also not be aware of potential teratogenic effects of many other substances, prescribed or not prescribed, that could harm their babies if taken during pregnancy.

Considering etiological factors of intellectual impairments and that 30 - 50% of cases have unknown etiology (Percy & Brown, 1999), it is conceivable that the effects of teratogens may be higher than previously estimated. The teratogenicity of many drugs have been classified and made available either through the U.S. Food and Drug Administration (FDA) pregnancy risk categories, or the Teratogen Information System (TERIS), which provides information for more than 2,800 agents and almost 200 commonly prescribed drugs (Gilstrap & Little, 1998). Both of these systems have categorized the risk of congenital malformations caused by prescription drugs. Thus, the public can be made aware of the risk of structural teratogenesis caused by particular drugs. However, many drugs can also cause behavioural teratogenesis, in which behavioural or neuropsychatric symptoms appear well after birth following in utero exposure to drugs or toxins (Ward & Zamorski, 2002). The behavioural teratogenicity of drugs is neither extensively researched nor explicitly categorized. One of the main reasons is that structural abnormalities as such are more easily observed in the newborn and can be easily categorized. That is, researchers and health care professionals can easily detect shortened or missing limbs, cleft palates, facial and other abnormalities. In contrast, behavioural abnormalities are not as apparent in the newborn because it is more difficult to test the neurodevelopmental profile of the neonate than those of a child (Nicholls, 2000).

Another reason that behavioural teratogenicity is not easily detected is due to the large variability in phenotypic expression in the developing child (Nicholls, 2000). That is, some drugs may produce neuropsychiatric

sequelae that are apparent only during adolescence and may resemble developmental delays. Prenatal ethanol (alcohol) exposure is a prime example that depicts a wide array of postnatal effects (Koren, 2001). At the inception of the term fetal alcohol syndrome (FAS), it was decided that moderate to large amount of alcohol consumption can lead to FAS and cause characteristic physical deformities and cognitive impairments, often seen in early childhood (Streissguth & O'Malley, 2000). Recently, however, the name fetal alcohol spectrum disorder (FASD) has been used to encompass diagnoses that include FAS, partial FAS (pFAS) and others. It is hypothesized that FASD encompasses the variety of symptoms and cognitive impairments seen with varying doses of prenatal alcohol consumption. For example, low doses of alcohol, insufficient to produce full FAS features, may nonetheless produce cognitive impairments, although subtle, intellectual and developmental delays associated with FASD may begin as the child enters the first years of schooling (Health Canada, 2003).

It is conceivable that intellectual and developmental delays may occur because pregnant mothers may be exposing their fetuses to yet unknown behavioural teratogens (Hoyme, 1990). Since many of the psychotropic drugs cross the placenta and affect brain neurotransmitters there is a definite risk of long-term consequences to the developing brain (Mortensen, Olsen, Bendsen, Obel & Sorensen, 2003). It has been estimated that one-third of women take psychotropic drugs at least once during their pregnancy (Nicholls, 2000). Recent evidence demonstrates psychomotor developmental delay in children prenatally exposed to at least one psychotropic drug (Mortensen et al., 2003). However, the risk of neurobehavioural delays is not well recognized or investigated. For example, the FDA has only recently (June 2004) recommended that antidepressant medication be labelled, cautioning pregnant women of the side effects on the newborn (FDA MedWatch Website, 2004; Richwine, 2004). However, other psychotropic medications are being prescribed to pregnant mothers without consultation of the risk to the neonate.

In reviewing literature concerning prenatal psychotropic drug exposure, this paper focusses on two key areas. First, past and current literature is cited describing human and animal data suggesting prenatal mechanisms by which these drugs may cause neurobehavioural consequences in the developing brain. Second, perinatal effects of psychotropic drugs will be discussed with respect to withdrawal symptoms.

Critical Periods in Human Development

Teratogens can pose harm during any of the three stages of development. During the first two weeks post-conception, the zygote is rapidly dividing and not yet implanted. At this point teratogens that pose the greatest risk will cause imminent death to the developing fetus (Macara, 2000). Once implanted, the next 5 weeks are called the embryonic period. During this period, organogenesis, the development of organs, begins. If the embryo is subjected to teratogens, major morphological changes (such as those caused by thalidomide) will occur because this is the stage of rapid cellular division and differentiation (Gilstrap & Little, 1998). Teratogens affecting the central nervous system (CNS) at this stage will probably cause neural tube defects (NTD) because the neural plate does not close properly thereby not forming the neural tube. During the fetal period, which begins in the 8th week of development, the CNS is very sensitive to teratogens, which can cause minor morphological abnormalities (such as neuronal migration disorders) or physiological defects (changes in synaptogenesis, neurogenesis). Thus, the human CNS is vulnerable to teratogenic effects throughout embryonic and fetal development.

Perinatal Events

The human CNS is very vulnerable perinatally (around the time of birth) to various exogenous factors such as teratogens, stress of delivery, physical injury, etc (Percy and Brown, 1999). Many of these factors produce insults termed perinatal events. Neonates at risk of birth complications are tested with the "Apgar" method of scoring asphyxia. This test measures appearance of neonate, pulse, grimace, activity and respirations for a total maximum score of 10. Several studies have shown a relationship between reduced Apgar scores and a significantly increased risk of developmental delays in neonates when followed up at various ages of childhood. For example, Stromme (2000) found that Apgar scores of 3 - 6 increased the probability of mental retardation in a study of Norwegian children. In a Denmark population, Holst, Anderson, Philip and Henningsen (1989) found that Apgar scores of 7 or less were adequate to become a predictor of mental retardation later in life. Perinatal events due to teratogens can occur because of neonatal drug withdrawal syndromes. For example, psychotropic drugs given in the third trimester produce withdrawal symptoms in the neonate seen up to a few weeks postpartum (Ward & Zamorski, 2002). These withdrawal symptoms include motor or sensory problems, asphyxia (causing low Apgar scores), sleep apnea, and seizures.

Psychiatric Disorders and Pregnancy

Mental illnesses are common in women during their childbearing years. Mood disorders such as anxiety and depression may be exacerbated by the onset of pregnancy and may ensue after delivery. The prevalence of depression can be as high as 10 - 16% during pregnancy (Laine, Heikkinen, Ekblad & Kero, 2003). The risk of relapsing into a post-partum depression can be very high depending on the level of depression and treatment course. For example, women who become depressed during pregnancy are at the highest risk of relapse into post-partum depression (Ward & Zamorski, 2002). Similarly, women who have bipolar or anxiety disorders are also at high risk for developing postpartum relapse. Thus, pharmacological treatment may be necessary in mental illness as an adjunct to other forms of therapy or mandatory and essential. Drugs currently prescribed for mental illnesses have a variety of effects on the fetus during pregnancy and delivery. It should be stressed that untreated psychiatric illnesses pose a tremendous threat to the fetus due to maternal behaviour and that discontinuing psychotropic drugs may also exacerbate maternal mental illnesses and cause secondary effects to the fetus. This review will focus on the effects of these drugs on the fetus from human and animal studies. Finally, a special section will focus on anticonvulsants because they are crucial to the control of epilepsy, but also because they are also largely prescribed as mood stabilizers (Lee, Inch & Finnigan, 2000).

Antidepressants

Antidepressant drugs are those given for minor or major depression, obsessive-compulsive disorder, bipolar disorder and various other related mental illnesses. Their mechanism of action usually involves increasing brain concentration of the biogenic amine/catecholamine neurotransmitters. For example first generation antidepressants called monoamine oxidase inhibitors (MAOI), inhibit the breakdown of serotonin, norepinephrin and dopamine. However, their side effects were much too strong and the effects non-specific. The second generation drugs called tricyclic antidepressants (TCA) blocked reuptake channels for serotonin and norepinephrin. Blocking the neuronal reuptake channel prevented degradation of the neurotransmitters thereby increasing their synaptic concentrations. In recent years, drugs have become more specific in blocking the serotonin reuptake and not norepinephrin. These third generation antidepressants are called selective serotonin reuptake inhibitors (SSRI). SSRI antidepressants tend to have even fewer side effects than TCA and fewer than MAOI.

Monoamine oxidase inhibitors (MAOI) are usually not indicated for use during pregnancy because of their adverse side effects. Gilstrap and Little (1998) point out the lack of case and epidemiological studies regarding effects of prenatal exposure of MAOI on rates of congenital malformations. The effect of MAOI on brain development comes from various rodent studies. Mejia, Ervin, Baker and Palmour (2002) administered inhibitors during gestation and lactation. They found that the mice exhibited significantly more aggression towards other mice. In another study, Whitaker-Azmitia, Zhang and Clarke (1994) administered the inhibitors during gestation to investigate the effect on the brain neurochemistry. They found reduced serotonergic innervation in the cortex.

Tricyclic antidepressants (TCA) are generally considered safe for use during pregnancy (Gilstrap & Little, 1998, Lee et al., 2000). The birth incidence of congenital malformations is not increased nor does there seem to be any alteration of brain anatomy based on human studies. Considering cognitive and behavioural assessments there seem to be no negative effects of prenatal TCA administration. For example, Simon, Cunningham and Davis (2002) used a prospective study to investigate the effects of prenatal TCA. The authors did not find any significant increase seizure incidence or delay in motor and speech development after prenatal exposure to TCA. However, these authors did not clarify the age at which the children were tested and it is assumed that they had not entered school. In another recent prospective study, Nulman et al. (2002) also investigated the effects of prenatal TCA exposure on child development. The authors of this study found no change in cognition, language development or behaviour in preschool or early school children.

Selective serotonin reuptake inhibitors (SSRI) may be among the most highly prescribed drugs in North America. SSRIs are far safer for human consumption than TCAs or MAOIs. Their pharmacokinetic properties afford them low prevalences of major side effects. Also, because they are relatively specific for the serotonin reuptake channel, they do not produce undesired CNS effects, often seen with MAOIs. However, as Koren (2001) points out, manufacturers of Prozac brand SSRIs, such as Eli Lilly, Ltd., suggest that the drug should not be consumed during pregnancy because its safety has not been properly documented. Despite this, SSRIs are still prescribed and indicated for use in moderate to severe depression during pregnancy (Lee et al., 2000). Several studies have found no increased risk of congenital malformations when using SSRIs during the first trimester (Koren, 2001; Kulin et al., 1998; Nulman et al., 2002). In another study, Chambers, Johnson, Dick, Felix and Jones (1996) investigated the outcomes of

fluoxetine on fetal anomalies. Similar to other studies, they found no association between fluoxetine and major structural abnormality. However, they found a significant difference of minor anomalies in fetuses prenatally exposed to fluoxetine as compared to controls. This study demonstrates that careful analysis must be performed so that minor anomalies will not be overlooked. With respect to cognitive development, Nulman et al. (2002) carried out a prospective controlled study using SSRI exposure throughout pregnancy. They found no increase in delay of cognitive or language development in pre-school or early school aged children. Similarly, Simon et al. (2002) found no increased risk of developmental delay or congenital malformations after SSRI exposure. However, a recent study by Casper et al. (2003) showed a different trend after SSRI exposure. In a well-controlled study, the children of depressed mothers exposed to SSRI or unexposed depressed mothers were followed up to age of 40 months. They found that children prenatally exposed to SSRIs scored lower on the psychomotor indexes of the Bayley Scales of Infant Development test and lower on the motor quality factor of the Bayley Behavioral Rating Scale. The authors suggest that subtle motor developmental delays may be one of the side effects of prenatal SSRI exposure. In another recent study, Zeskind and Stephens (2004) used a systematic prospective study to investigate the prenatal effects of SSRIs on newborn neurobehaviour. They found that infants were hyperactive, tremulous and had behavioural state abnormalities. The aforementioned human studies demonstrate that gestational exposure to SSRIs cause behavioural abnormalities in infants and possibly in later childhood. Studies in which animals were prenatally exposed to SSRIs also show minimal cognitive deficits. For example, Vorhees et al. (1994) found that prenatal fluoxetine found no effects on locomotor activity, behaviour paradigms or cognitive performance. Similarly, Coleman, Christensen, Gonzalez and Rayburn (1999) administered paroxetine prenatally to mice. The authors found no major behavioural effects of exposed mice. However, they did find that male mice were more aggressive and vocal at various times, which may suggest heightened anxiety.

Adverse effects of prenatal antidepressant exposure on the fetus may be secondary to effects of drugs. Both TCA and SSRIs are known to cause neonatal withdrawal symptoms when these drugs are used during the third trimester of pregnancy and especially nearing delivery. Symptoms associated with antidepressant withdrawal are collectively called neonatal withdrawal syndrome or neonatal discontinuation (Haddad, 2001; Lee et al., 2000). Withdrawal symptoms associated with prenatal antidepressants include: irritability, tremulousness, diarrhoea, poor feeding, respiratory distress and seizures (convulsions). These symptoms can occur in patients

taking therapeutic or larger doses. Withdrawal can begin in as little as 72 hours post-partum and last for several days (Lee et al., 2000). Chambers et al. (1996) investigated birth outcomes after administration of fluoxetine during each of the three trimesters. Infants exposed during the third trimester had significantly increased risk of premature delivery and admission to special care nurseries as compared to those exposed during the first two trimesters. Infants exposed late in gestation also had lower birth weights and were generally shorter in length. Most importantly, infants showed neonatal withdrawal symptoms including respiratory difficulties, cyanosis on feeding and jitteriness. In a recent case study of 5 women, Nordeng, Lindemann, Perminov and Reikvam (2001) investigated neonatal withdrawal symptoms in women taking other SSRIs (paroxetine, citalopram and fluoxetine) taken as monotherapy within the therapeutic dose. Neonatal withdrawal symptoms included irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties and convulsions. The authors found that symptoms started as early as delivery and lasted for up to one month. In all these cases, APGAR scores were between 8 and 9 after 1 minute.

In another recent study, Laine et al. (2003) used a prospective controlled study of 20 mothers taking either fluoxetine or citalopram during the third trimester. The authors measured neonatal withdrawal symptoms, using the term serotonergic symptoms, and measured levels of monoamines in the umbilical cord. Compared to control infants, those exposed to SSRIs had progressively lower Apgar scores at 1, 5 and 15 minutes, becoming significant only at 15 minutes. SSRI exposed infants also had a significant 4-fold increase in serotonin symptoms versus controls occurring in the first 4 days of life. These symptoms include myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination, and rigidity. Measuring the levels of monoamines in the umbilical vein, the authors found that serotonin (5-HT) and its metabolite (5-HIAA), dopamine metabolite (HVA), and noradrenalin were all significantly reduced. In another study by Costei, Kozer, Ho, Ito and Koren (2002), 55 neonates exposed to paroxetine in the third trimester were examined for withdrawal symptoms. The authors found a significant increase in respiratory distress, hypoglycemia, and jaundice when compared to neonates exposed in the first two trimesters or unexposed neonates. The authors found that the discontinuation syndrome began shortly after birth and lasted for up to 1 month. Simon et al. (2002) investigated the perinatal effects of antidepressant use. They found that SSRI but not TCA exposure caused a significant decrease in Apgar scores at 5 minutes. Using different analysis of the Apgar data the authors looked at the number of infants who scored less than 5 at 1 minute and less than 7 at 5 minutes. They found that more SSRI exposed infants scored less than 5 and less than 7 at 1 and 5 minutes,

respectively. Further, the authors investigated the effect of time of exposure of SSRI on Apgar scores. They found that third trimester exposure yielded significant decreases in Apgar at both 1 and 5 minutes. Interestingly, the differences at 1 and 5 minutes were 0.83 and 0.47, respectively out of possible 10. The authors of this paper also investigated developmental delays. Although they found no significant differences, their data does show increased motor delay in SSRI exposed group, and also increased seizure occurrence in both SSRI and TCA exposed groups.

It would be informative to analyze the relationship between those exposed during the third trimester that had low Apgar scores and their risk of having developmental delays or seizure disorders. This idea is reiterated in the study of mental retardation etiology published by Stromme (2000). The author describes analysis of Norwegian children displaying mental retardation and the prenatal/perinatal factors that may contribute to etiology. Decreased birth weight and Apgar scores between 3 - 6 at 1 and 5 minutes were associated with increased risk of mental retardation. Similarly, Krebs, Langhoff-Roos and Thorngren-Jerneck (2001) used a population-based follow-up of children with low Apgar scores. The authors found that children with Apgar scores below 7 at 5 minutes had significantly more speech/language deficits.

Although low Apgar scores predispose infants to motor and cognitive developmental delays, it should be noted that low and extremely low Apgar scores were investigated in the aforementioned articles. Most authors did not distinguish the important levels 6 - 8. This level may be critical for future development especially considered with other neonatal withdrawal symptoms. Further, it would seem that 0.5 - 1 full point decrements in Apgar scores would make a large difference and should be scrutinized. Perhaps these studies did not have the proper sensitivity in protocols to discriminate small differences in Apgar scores. It would be crucial for future studies to focus on perinatal events, such as those that cause Apgar scores and neonatal withdrawal symptoms. Protocols should be set in place to clearly label all symptoms and characteristics of the neonate so that future follow-up studies could properly describe cognitive and neurodevelopmental milestones with greater accuracy.

Anxiolytics

Benzodiazepines are one of the most frequently used drugs to treat anxiety, and among the most commonly prescribed drug to women (Iqbal, Sobhan & Ryals, 2002). Benzodiazepines (BZD) exert their main function by acting on

the gamma-amino butyric receptor A (GABA A receptor) in the brain (GABA is an inhibitory neurotransmitter). Apart from being used to treat various anxiety disorders, benzodiazepines are also used for sedation, light anaesthesia during surgery, anticonvulsants, muscle relaxants, and insomnia. According to Koren (2001), 2% of pregnant women may be on BZD. Considering that half of all pregnancies are unplanned, there must be a strict concordance about the long-term effects of BZD use during pregnancy. The teratogencity of BZD remains a controversial topic among prenatal drug exposure. A recent meta-analysis by Koren (2001) showed that there was no risk of major congenital malformations associated with BZD use. However, when the analysis was done on case studies alone, the authors found a significant increase in risk of major malformation or cleft palate/lip.

Several studies have suggested that prenatal exposure to BZD may produce the "benzodiazepine syndrome" (Gilstrap & Little, 1998; Iqbal et al., 2002). This syndrome consists of facial dysmorphism (slanted eyes and epicanthal folds), hypotonia and delayed motor development, polycystic kidney, sub-mucous clef hard palate, microcephaly, varying degrees of mental retardation, convulsions, and neonate abstinence syndrome. The hypothesis originally posited by Laegreid, Olegard, Walstrom and Conradi (1989) likens the characteristics of benzodiazepine syndrome to fetal alcohol syndrome. Although the publication was based on case studies, the authors measured blood levels of BZD and confirmed that elevated levels were obvious after regular therapeutic usage of BZD. The same authors followed up various infants prenatally exposed to BZD to assess their neuro-cognitive development. Laegrid (1990) followed up children prenatally exposed to BZD and highlighted the following characteristics: microcephaly (n = 2), severe mental retardation (n = 2), mild mental retardation (n = 5) and normal intelligence (n = 1). In a prospective study, Laegreid, Hagberg, and Lundberg (1992a) followed 17 children prenatally exposed to therapeutic doses BZD as the only psychotropic drug and compared to children unexposed to any psychotropic drug. The authors found that BZD exposed children deviated in neurodevelopmental tests. Gross motor and fine motor development was delayed at 6 and 10 months follow-up. At 18 months follow-up fine motor control was still delayed and children had muscle tone deficits compared to the control group. The same group of children were followed up for cognitive testing in another study (Viggedal, Hagberg, Laegrid & Aronsoon, 1993). The authors used the Griffith's Developmental Scale which measures Locomotor, Hearing and Speech, Eye and Hand Coordination, Performance, Practical Reasoning, and Personal-Social. They found that BZD exposed children consistently scored lower on the general quotient (G.Q.) at 10 and 18 months.

In another study, Laegreid, Hagberg and Lundberg (1992b) hypothesized that the effects of prenatal BZD use on neurological development might stem from drug intoxication and neonatal withdrawal symptoms. Indeed, the authors found infants exposed to BZD had lower birth weights, shorter birth length, and had significantly more perinatal complications than their unexposed control groups. Neonatal withdrawal symptoms after BZD exposure are well documented for variety of BZD drugs (Gilstrap & Little, 1998; Iqbal et al., 2002). Neonatal withdrawal symptoms included: low Apgar scores, hypertonia, irritability, abnormal sleep patterns, constant crying, tremors, myoclonus, bradycardia, cyanosis, suckling difficulties, apnea, feeding aspirations, diarrhea, vomiting, and growth retardation. When diazepam and other BZDs are administered close to delivery, the neonates are given the label "floppy infant syndrome." The characteristics of this syndrome include withdrawal symptoms (mentioned above), hypothermia, lethargy, respiratory problems and feeding difficulties. Although the authors claim that infants recover without long-lasting effects, it is likely that these withdrawal symptoms could cause some types of neuro-cognitive developmental delays.

Animal studies also show immediate and long lasting effects of prenatal BZD exposure. Rats prenatally exposed to diazepam had significant deficits in acquisition and retention of spatial discrimination task (Jaiswal & Bhattacharya, 1993). Alprazolam, another commonly used BZD given prenatally to either mice (Christensen, Gonzalez & Rayburn, 2003) or rats (Jaiswal, 2002) produces significant increases in anxiety in offspring when tested as juveniles or adults. Because BZD acts by activating GABAA receptors, it is suspected that increased anxiety is indicative of GABAA receptor desensitization. Indeed, Nicosia et al. (2003) found that male rats had long lasting behavioural deficits and were hypersensitive to convulsants such as pentylenetetrazol (GABAA antagonist). In contrast, female rats showed increased resistance to seizures. The complex nature of prenatal BZD exposure on cognitive and behaviour seems to depend on gender, at least in animals.

Human fetuses should be sensitive to BZD throughout fetal development since the density of GABA A receptors is continually increasing, and animal studies have shown that chronic BZD use reduces the number and density of GABA A receptors in the brain. Using aborted fetal brains, Reichelt et al. (1991) found that receptors appeared in the human brain as early as 8th week of gestation. The density of GABA A receptors steadily increased throughout the gestational period. In another study, Hebebrand et al. (1988) found that GABA A receptor density steeply increased in the whole brain between 8

and 11 weeks of gestation, and in the frontal cortex receptor density increased between 12 and 26 weeks of gestation. Livezey, Marczynski and Isaac (1986a, b) found that prenatal diazepam caused chronic anxiety in the adult rat and cat offspring and that this was related to a reduced number of receptors in the brain. These effects, if true in human cases, may explain the long term behavioural and cognitive effects often observed in prenatal BZD exposure.

Anticonvulsants

Around 0.5 - 1% of all pregnancies occur to women with some form of epilepsy (Gilstrap & Little, 1998). In these cases, the patients do not have a choice about the prenatal exposure to drugs because anti-epileptic drugs (AED) are essential to daily living (Dean et al., 2002). Use of AED during pregnancy increases the risk of congenital malformation about 2 to 3 fold. The exact mechanisms by which these occur depend on the type of AED. The increased malformation has been shown not to be related to the maternal epilepsy per se, but rather to the AED. Epileptic mothers not using AED generally have the same rate of malformations as non-epileptic mothers. Further, epileptic mothers using AED have just as high a malformation rate as non-epileptic mothers using AED as mood stabilizers (Meador, 2002). Older anticonvulsants are known teratogens, and although newer AED may have better pharmacokinetic profiles, their effects on pregnancy are still unknown.

Some of the older AED with known profiles of teratogenicity include phenytoin, carbamazepine, and valproate. Phenytoin has been used for more than 50 years as an AED and has been one of the most commonly prescribed anticonvulsant. The effects of phenytoin on the fetus have been termed fetal hydantoin syndrome because of characteristic malformations that occur. Some of the congenital malformations include cleft lip/palate and other craniofacial anomalies, limb defects, and some learning deficiencies. In a few studies it was found that children exposed to phenytoin prenatally had 10-point decrease in I.Q., although this was not considered mentally retarded (Gilstrap & Little, 1998). In a recent review by Meador (2002) studies on prenatal AED show that phenytoin has adverse effects on neurobehavioural development. Various animal studies also show similar trends. For example, prenatal phenytoin exposure in rats caused long term spatial (Morris and radial arm maze) and working memory (delayed non-matching to sample) deficits in the offspring (Tsutsumi, Akaike, Ohno & Kato, 1998). Schilling, Inman, Medford, Moran and Vorhees (1999) extended the findings to include deficits in reference memory based spatial learning deficits using cued platform learning and spatial discrimination tests.

Using carbamazepine prenatally results in consequences similar to those of phenytoin. Craniofacial, limb anomalies, learning disabilities and neural tube defects have been summarized as the fetal carbamazepine syndrome. In one study verbal I.Q. was reduced by 10 points (Meador, 2002). However, in a recent study Gaily et al. (2004) found no difference in verbal and non-verbal I.Q. scores of children prenatally exposed to carbamazepine. Using valproate prenatally increases the risk for neural tube defects, various craniofacial malformations and congenital heart defects, but no cognitive dysfunction (Gilstrap & Little, 1998). However, Koch et al. (1996) found that valproate caused immediate neonatal withdrawal symptoms such as hyperexcitability causing neurological deficits. When examined 6 years later, the children continued to have long-term neurological dysfunctions. In a recent clinical study of 57 children prenatally exposed to AED, around 77% of children had developmental delay, most cases (80%) having had prenatal exposure to valproate alone or in combination with another AED (Moore et al., 2000).

In the aforementioned study by Moore et al. (2000), the effects of prenatal AED exposure were not differentiated by type of drug, but rather grouped in a clinical diagnosis of fetal anticonvulsant syndrome. Interestingly the authors found that 44 of 57 (77%) had learning difficulties, 81% had speech delay, 60% gross motor delay and 42% fine motor delay. Interestingly, of the school aged children, 74% were enrolled in special education or receiving learning support. Considering behavioural problems, 81% of cases reported some type of behavioural dysfunction. Of these, 60% had some autistic features, 39 % had hyperactivity, but only a few were actually diagnosed with autism or Asperger syndrome. Although the authors report 19% birth incidence of neonatal withdrawal (including seizures and jitteriness), this was not discussed at length or compared to the current neurodevelopment profile. Furthermore, the authors failed to separate the data based on particular AED exposure, which would have been more informative considering mechanistic differences amongst the drugs. Nevertheless, this study is one of the pioneering case studies investigating the long term neurodevelopmental profiles of prenatal AED exposure.

In a recent comprehensive paper, Dean et al. (2002) used a retrospective study to investigate the neonatal effects and long-term consequences of prenatal AED exposure. Based on hospital records they found significant neonatal withdrawal symptoms after exposure to valproate and phenytoin and polytherapy (more than one drug). Neonatal withdrawal was defined as having the following: jitteriness, hypotonia, seizures, apnoeic episodes, hypoglycemia and feeding disorder. The authors further investigated

prenatal exposure on developmental delays and found significant adverse outcomes after treatment with carbamazepine, valproate, phenytoin or polytherapy. In all cases, speech delay was the most common developmental disability. When looking at behavioural disorders (autism spectrum, ADHD) associated with normal development, the authors found significant effects after exposure to carbamazepine, valproate and polytherapy. Although the authors did not find a link between neonatal withdrawal symptoms and cognitive dysfunction, this study is one of the first, and does not rule out a possible link.

How Drugs Exert Teratogenic Effects

As pharmaceutical companies design drugs to become more permeable to the blood brain barrier, they will inevitably cross the placenta and enter the fetal brain as well. Highly prescribed drugs such as fluoxetine and diazepam have been investigated and researched thoroughly. Although their safety profile shows little or no risk for major congenital malformations (Gilstrap & Little, 1998), their effects on neuro-cognitive development is far from being completely understood. Antidepressants, anxiolytics and antiepileptics act on neurotransmitter systems that are being shaped as early as the 5th and 8th week of gestation for serotonin and GABA, respectively (Herlenius & Lagercrantz, 2001).

The effects of drugs on cognitive and neuro-development can occur via two main pathways. First, drug specific actions on the developing brain alter brain neurotransmitter levels, change receptor levels and ultimately alter brain circuitry. For example, Cabrera-Vera and Battaglia (1998) found that prenatal exposure to fluoxetine changed the levels of serotonin reuptake in prepubescent age. In various limbic regions such as the hippocampus and amygdala, which are vital for learning and emotions, reuptake channels were upregulated. In contrast, Montero, de Caballos and Del Rio (1990) found that various antidepressants, including fluoxetine, downregulated the reuptake channel in the cerebral cortex of the rat that lasted until adulthood. These data suggest that various molecular changes occurring in the brain after prenatal drug exposure may have functional consequences in later life.

The second pathway of prenatal drug exposure on cognitive neuro-development is via perinatal complications. All of the antidepressants, anxiolytics and antiepileptics mentioned above caused some form of neonatal withdrawal symptoms even when parental exposure was within the therapeutic dose. The most common neonatal withdrawal symptoms included a motor component, displaying as jitteriness, tremors, irritability,

hypo/hypertonus, and hyperreflexia. The exact consequence of these motor manifestations is unknown but it is likely to have some gross/fine motor developmental delay as been shown for prenatal exposure of BZD (Laegrid et al., 1992) and antiepileptic drugs (Moore et al., 2000). However, in all three drug classes, convulsions and seizures seem to be some of the more severe neonatal withdrawal symptom. It is possible that infants may have minor convulsions (such as cyclonic jerks), which may not be identified but instead classified as a motor manifestation (jitteriness, tremor etc.). The situation is further complicated because neonatal withdrawal symptoms may become apparent several days post-partum and can last up to one month. Thus, parents who take their newborns home one day post-partum may not be aware or attentive to possible neonatal withdrawal symptoms. In some cases, parents will return to the hospital and admit the infant to the hospital for these symptoms. The lag in treatment and lack of constant supervision during those few critical days post-partum may have unknown consequences on fetal development.

Withdrawal symptoms can include cyanosis, apnea, respiratory and sleep difficulties. It is very probable that these processes contribute to low Apgar scores. Holst et al. (1989) assessed the neonatal risk factors associated with handicap (developmental disability) in later life. The authors found that intrapartum asphyxia was a strong predictor of developmental disabilities in childhood. The authors described asphyxia as Apgar scores of less than 7 at 1 minute and less than 10 at 10 minutes. Many of the neonates prenatally exposed to SSRIs or BZD in third trimester all had reduced Apgar scores as compared to unexposed children, which may have put them at risk for developmental disabilities in later life. The authors also describe low birth weight and early gestation as a strong predictor of delays in development. In the study by Chambers et al. (1996), neonates exposed to SSRIs during third trimester have increased risk of premature delivery and lower birth weights. Similar results have been shown for prenatal exposure to BZD (Laegrid et al., 1992).

Conclusions

Although mental illnesses and epilepsy cannot be ignored and untreated especially in pregnant women, some caution should be exercised. Close monitoring of drug dosages and blood levels of metabolites should indicate that therapeutic doses are maintained. Further, psychotropic drugs given to pregnant women should be given according to their pharmacokinetic profiles. For example, drugs with longer half-lives and active metabolites

are preferred to those with longer half-lives and no active metabolites (Iqbal et al., 2002). Drugs with shorter half-lives will be excreted at a faster rate and are more likely to produce withdrawal symptoms. Active metabolites prolong the effect of the drug in the brain and thus minimize the risk of withdrawal symptoms post-partum. Withdrawal symptoms can be reduced by reducing the tapering the mother off the drug near time of delivery. However, caution should be exercised that the mother's mental illness does not relapse. Until more is known about the effects of these drugs on the neonates, unnecessary usage of psychotropic drugs should be eliminated or reduced dramatically and supplemented with psychiatric therapy.

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Correspondence

Eduard Bercovici, BSc, MSc
Office of Student Affairs
Faculty of Medicine, University of Toronto
1 King's College Circle, Room 2171B
Toronto, Ontario M5S
Tel: 647-290-8037
Fax: 416-971-3056
E-mail : eduard.bercovici@utoronto.ca