REVIEW ARTICLE

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Treatment of Anxiety During Pregnancy

Effects of Psychotropic Drug Treatment on the Developing Fetus

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Contents

Abstract

Pregnancy is a time of great emotional change for a woman, producing increased stress and anxiety. Medication may be required for the treatment of anxiety disorders at this time. Given the fact that psychotropic drugs readily cross the placenta and could have important implications for the developing fetus, it is necessary to balance the possible effects of medication against the potential effects to both the mother and fetus if the anxiety disorder is left untreated.

Despite the widespread use of psychotropic drugs such as benzodiazepines and antidepressants during pregnancy, there is a paucity of information regarding the effect of such exposure on the developing fetus.

From a review of the literature it is clear that the issue of safety of psychotropic drugs during pregnancy is far from resolved. While some of the findings from animal studies are alarming, these studies cannot be directly extrapolated to humans. In addition, varying sample sizes and multiple drug exposures further complicate interpretation of human studies.

Nonpharmacological treatments such as cognitive behavioural therapy should be employed whenever possible for the treatment of anxiety disorders during pregnancy. However, if medication is required pregnant women should be prescribed the lowest dosage for the minimum amount of time.

Pregnancy is a time of extreme change for a woman. Marked changes in gonadal steroid levels have been reported, with as much as a 100-fold variation in oestrogen serum levels and a 1000-fold change in progesterone serum levels.[1] Such hormonal changes may leave the woman with feelings of stress and anxiety.

Psychological factors may also have an important role to play in the development of anxiety disorders at this time. Often the expectant mother has concerns over the health of the child, the change in lifestyle likely to occur in her own life after the birth of the child, her own ability to be a good mother and for many, financial worries may be a major concern. There are also instances where the pregnancy is unexpected or unwanted, which may further increase the stress and anxiety experienced at this time. In addition, for some women pregnancy may bring to mind painful events in the life of the woman with her own parents – the 'ghosts in the nursery' phenomenon.[1,2] There is some evidence to suggest that panic disorder may be related to adverse childhood experiences,[3] and it is therefore possible that such women may be more vulnerable during pregnancy to this phenomenon.[1]

Although it is obvious that pregnancy alone may produce states of anxiety, the question has been raised as to what happens to pre-existing anxiety disorders during this period. Most of the literature in this area has focused on the effect of pregnancy on pre-existing panic disorder and obsessive compulsive disorder to the exclusion of other disorders such as generalised anxiety disorder and post-traumatic stress disorder.

1. Panic Disorder

Although childbirth may lead to the onset of panic disorder in some cases,[4] research into the effect of pregnancy on pre-existing panic disorder has revealed mixed results. Several studies have reported that approximately 50% of patients report an alleviation of their symptoms during pregnancy.[5,6] Others have found similar results, but reported a return of symptoms in the postpartum period.[7,8] In addition, no change in symptomatology[9,10] or a worsening of panic symptoms[5,6] have also been demonstrated. However, it is possible that these results reflect differing panic disorder populations. Cohen et al.,[5] reported that women with milder panic symptoms may experience an improvement in symptoms during the pregnancy period, but that in women with more severe symptoms, pregnancy may produce an exacerbation of panic disorder.

2. Obsessive Compulsive Disorder

Several groups examining the precipitating factors for the onset of obsessional states have reported that pregnancy and childbirth appeared to be one of a number of precipitants.[11-14] However, in women with pre-existing obsessive compulsive disorder, some researchers report a worsening of obsessional symptoms during the pregnancy,[15,16] whereas others have either reported no change, or an improvement in obsessional symptoms.[16] The differing results reported might be explained by the severity of symptoms prior to the pregnancy. However, a sufficiently large cohort of patients has not been studied in order to elucidate the determinants of change of clinical status during pregnancy.

3. Psychotropic Drug Treatment and Pregnancy

It has been shown that benzodiazepines and antidepressants are the most commonly prescribed drugs for the treatment of anxiety disorders and that benzodiazepines are the most widely prescribed psychotropic drugs,[17] with diazepam being the single most prescribed (84%).[18] Benzodiazepines have been reported to be effective in the treatment of generalised anxiety disorder and phobic situations.[19] They have been shown to be effective in the treatment of panic disorder; however; monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which are also effective, are often used. In regard to obsessive compulsive disorder, selective serotonin (5-hydroxy tryptamine, 5-HT) reuptake inhibitors (SSRIs) have been reported to be the drugs of choice.[20]

3.1 Pharmacological Treatment versus Nonpharmacological Treatment

One of the greatest problems facing psychiatrists is the necessity of balancing the possible effects of psychotropic medication on the developing fetus against the potential detrimental effects to both the mother and the fetus if the anxiety disorder is left untreated.[1,21] Wherever possible, behavioural techniques such as cognitive behavioural therapy should be employed for the treatment of women with anxiety disorders during pregnancy. Such techniques have been reported to be effective in the treatment of panic disorder during the pregnancy period.[22,23] Failure to treat anxiety disorders during pregnancy may have adverse effects on the developing infant. There is evidence to suggest that stress and anxiety during pregnancy can have an adverse effect on birth outcome with decreased birthweight,[24-28] decreased gestational age at birth[24,28,29] and altered Apgar scores[29] reported. However, despite these findings some researchers have failed to find any association between maternal anxiety and pregnancy complications or fetal anomalies.[30-33]

In many cases nonpharmacological treatment methods are ineffective and medication is required. In addition, the mother may be unaware that she is pregnant while receiving psychotropic medication. This has important implications for the developing fetus, since drug exposure *in utero* is far more dangerous to the fetus, than exposure later in life, since the fetus lacks the ability to metabolise and eliminate drugs entering its biosphere.[34]

All psychotropic drugs readily cross the placenta and, despite their widespread use, information on the effect of exposure to psychotropic drugs on the developing fetus is incomplete.[35] However, in cases where an effect has been observed, psychotropic medication has been reported to affect the fetus in 3 main ways: organ malformation (teratogenicity); neonatal toxicity (perinatal syndromes); and postnatal sequelae (behavioural teratogenicity).[35] Despite the potential toxic effects of psychotropic medication on the developing fetus, relatively little attention has been given to this problem, most likely because of ethical, clinical and legal problems that would arise when treatment and research involve the fetus.[1]

If medication must be used during pregnancy, it is best to prescribe drugs that have been researched and evaluated for possible adverse effects and to use the lowest possible dosage for the shortest length of time.

4. Benzodiazepine Treatment and Pregnancy

4.1 Animal Toxicity and Teratogenicity

Several studies have examined the effect of benzodiazepine exposure in animals in terms of toxicity and teratogenicity (see table I). Studies conducted in the 1970s and early 1980s reported an association between benzodiazepine exposure *in utero* and fetal toxicity. This was demonstrated by decreased fetal bodyweight,[42,47] increased mortality and abortion rates[41,50] and decreased postnatal survival[42] following *in utero* exposure to benzodiazepines. Despite these findings, some later studies failed to find such an association.[51]

Fetal abnormalities have also been reported following benzodiazepine exposure[38,49,50] with an increase in the incidence of cleft palate,[40,46] exencephaly and limb anomalies[45] as well as rib defects at higher doses.[47]

Vorster et al.,[52] assessed the effect of exposure to diazepam on the development of chick embryos. When examined on the eighth day of development, the embryos displayed subcutaneous haemorrhage, prominent blood vessels on the lateral body wall, absence of a ventral body wall and anopthalmos. The incidence of these anomalies was dose dependent with 35, 43, 73 and 100% of embryos affected following exposure to diazepam 3.3, 5, 10, and 20μg, respectively. None of the control group showed any gross anomalies.

Ramamurthy and Chaudhry[44] found no teratogenic effects using intraperitoneal diazepam at doses of 4.5 to 5.5 mg/kg on gestational days 11, 12 and 13 in hamsters. However, the higher doses

Table I. Effect of benzodiazepine exposure on fetal toxicity and teratogenicity – animal data

Reference	Method	Results
Owen et al.[36]	Rats treated with oxazepam (0.03 or 0.06%) in their diet from GDs 8 to 16	Increased incidence of stillbirths and decreased pup survival were reported
Beall[37]	Both rabbits and rats treated daily with diazepam (20 or 80 mg/kg orally)	No evidence for increased risk of malformations in the offspring
Walker & Patterson[38]	Mice were administered chlordiazepoxide, barbital (barbitone), diazepam, chlorpromazine, hydrozine, pentobarbital (pentobarbitone)	Teratogenic effects were evident following exposure to barbiturates and tranquillisers
Brunard[39]	Treated pregnant mice, rats and rabbits with either tetrazepam, chlorazepate or nitrazepam and examined for potential teratogenic effects among the offspring	No teratogenic effects were evident in any group
Miller & Becker[40]	Treated pregnant rats with diazepam	Reported an increased incidence of cleft palate in the drug-treated animals particularly at the higher doses
Stenchever & Parks[41]	Treated mice with diazepam 0.2 mg/kg either in early (GDs 1 to 9) or mid (GDs 5 to 12) pregnancy	A decreased incidence of continued pregnancies was evident in animals exposed to diazepam in mid-pregnancy. Litter size, number of resorption sites and incidence of gross anomalies were unaffected
Guerriero & Fox[42]	Pregnant mice were exposed to 1 of 6 different benzodiazepines	Decreased birthweight and postnatal survival of the offspring was noted
Tuchmann-Duplessis[43]	Animals were exposed to either bromazepam, flurazepam or triazolam	No teratogenic effects of these drugs were observed
Ramamurthy & Chaudhry[44]	Assessed the effect of exposure to intraperitoneal diazepam 4.5-5.5 mg/kg from GDs 11 to 13 on the developing fetus	Toxic effects were evident at the higher doses with increased maternal death, reduced fetal bodyweight and increased incidence of resorption reported
Shah et al.[45]	Hamsters were treated with a single oral dose of diazepam 30-100 mg/kg or an intravenous dose of diazepam 5-10 mg/kg, on days 8-11 of gestation	Maternal and fetal toxicity was evident at higher doses. Fetal malformations were observed including cleft palate and exencephaly
Barlow et al.[46]	Looked at the association between diazepam and the incidence of cleft palate	Found increased incidence of cleft palate
Buttar[47]	Exposed rats *in utero* to chlordiazepoxide 10, 25, 50 and 100 mg/kg	No abnormalities were found at lower doses, decreased fetal weight and rib defects were evident at the higher doses
Corwin & DeMeyer[48]	Rats were exposed to chlorazepate 32 mg/kg on GDs 8 to 10	No malformations were found
Gill et al.[49]	Single injection of diazepam 120-980 mg/kg or chlordiazepoxide 280-3100 mg/kg on GD 8	A dose-related increase in fetal malformations were found in both groups, including encephaly and cranioschisis
Alleva et al.[50]	Treated mice on days 12-16 of gestation with oxazepam 0, 5, 15 or 50 mg/kg twice daily	Behavioural development was altered in a dose-dependent manner, with alterations reported in righting reflex, limb placing and auditory startle. These changes were maximal at 2 weeks of age. The highest dose also produced a significant decrease in locomotor activity evident at 60 days of age
Cagiano et al.[51]	Rats received a single daily injection of diazepam 0.1 and 1 mg/kg over GDs 14 to 20	No differences in neonatal mortality or weight gain were found
Vorster et al.[52]	Chick embryos were exposed to diazepam 3.3, 5, 10, 20μg at 48 hours of development. The embryos were sacrificed on the eighth day of development and examined for anomalies	Numerous abnormalities were reported such subcutaneous haemorrhage, prominent blood vessels on the lateral body wall, absence of ventral body wall and anopthalmos

GD = gestational day.

caused maternal death, reductions in fetal bodyweight and a higher incidence of resorption.

Despite these findings, many other researchers have failed to find any association between benzodiazepine exposure and fetal toxicity.[37-39,43]

Differences in sample size, the duration of exposure, the type of benzodiazepine administered and the species of animal used may account for the lack of consistent findings regarding the potential teratogenic effects of prenatal benzodiazepine exposure in the above studies.

Many of the abnormalities caused by teratogenic drugs are evident at birth. However, some are not immediately obvious and may only occur several months or even years following birth, such as diethylstilboestrol-induced vaginal adenocarcinoma.[34] Therefore, both the short and long term effects of prenatal benzodiazepine exposure on children need to be addressed.

4.2 Animal Behavioural Toxicity

Prenatal benzodiazepine exposure has been shown to produce a variety of effects on animals including behavioural toxicity. These effects may not be immediately evident at birth and are only detected as the animal develops. Deficits have been found in learning and memory behaviour, such as maze learning[53-55] and the acquisition of a conditioned avoidance response.[56] Alterations in locomotor activity have also been seen,[51,57-60] with animals displaying a lack of the locomotor activity burst which is evident in control treated animals within the first 2 to 3 weeks of postnatal development. Several researchers have found alterations in the social development of the animals[61,62] with increased threat and attack behaviour[63] and heightened emotionality and anxiety in benzodiazepine-exposed offspring.[62]

In addition, early development has been shown to be impaired in animals exposed to benzodiazepines[61,64] or the benzodiazepine inverse agonist, 6,7-dimethoxy-4-ethyl-beta carboline-3-carboxylate (DMCM) in some studies,[61] but others have reported no detrimental effects on postnatal development[46] or reported short term effects which were attenuated or disappeared within 2 weeks reportedly reflecting a temporary retardation of body growth.[50]

The results of these studies suggest that benzodiazepine exposure during pregnancy may produce behavioural deficits in animals which may not be evident until adulthood (table II).

4.3 Human Toxicity and Teratogenicity

With the knowledge that benzodiazepines may adversely affect animals during pregnancy, the effect of these drugs on the developing human fetus is of great importance (see table III). A significant association has been reported between benzodiazepine exposure in the first trimester of pregnancy and the development of fetal abnormalities such as oral cleft and cleft palate.[66-68] Diazepam was one of the most frequently implicated drugs associated with these abnormalities, with a 4-fold increase in cleft lip with or without cleft palate reported among children whose mothers had used diazepam in the first trimester of pregnancy.[67] This, however, may reflect the fact that diazepam accounts for approximately 70% of drug exposures during pregnancy.[18] Teratogenic effects have also been reported following exposure to meprobamate and chlordiazepoxide.[69,72]

Other malformations which have been reported to occur following benzodiazepine exposure include abnormalities of the abdomen, feet and toes, skeletal abnormalities, deformities of the lung, heart, gastrointestinal tract and the kidney[70] and muscle weakness.[71] Embryofetopathy, a condition similar to fetal alcohol syndrome, has been reported[71] with dysmorphism and central nervous system dysfunction also reported in these children.[71]

In contrast to these findings, a number of studies have reported no association between exposure to benzodiazepines and the development of fetal abnormalities.[73,74] Rosenberg et al.,[75] reported that exposure to diazepam in the first trimester of pregnancy was not associated with an increase in the birth of children with oral cleft. In addition, an increased risk among children already at a higher risk

Table II. Effect of benzodiazepine exposure on behavioural development – animal data

Reference	Method	Results
Hoffeld et al.[57]	Sprague-Dawley rats were administered either reserpine (0.1 mg/kg), meprobamate (60 mg/kg) chlorpromazine (6 mg/kg) or distilled water. The animals were injected 3 times/day in either early, mid- or late-pregnancy. Behavioural testing of the exposed offspring began at 97 to 98 days of age	A significant increase in locomotor activity on the running wheel was evident in the offspring of the reserpine and chlorpromazine exposed animals compared with the offspring of meprobamate exposed animals and control animals
Hoffeld et al.[57]	In a second experiment animals, were treated as above. However, behavioural testing of the offspring of these rats began at 35 days of age and continued until 77 days of age. In a third phase of the experiment, the animals were food and water deprived at 84 days of age followed by 40 trials of a strong unavoidable shock paired with a light and buzzer. Following this part of the experiment the animals were immobilised in wire mesh	No significant differences in emotionality were evident between the groups. No differences in the number of ulcers was observed between the groups. Reduced general activity was evident in the offspring of meprobamate exposed animals compared with the offspring of both control and reserpine-treated animals. These effects on locomotor activity were more evident in offspring exposed to drugs mid-pregnancy
Ljubimov et al.[56]	Administered diazepam to pregnant rats throughout gestation	The offspring of exposed animals exhibited altered sexual maturity as well as deficits in the acquisition of a conditioned avoidance response
Barlow et al.[46]	Rats were exposed to restraint stress alone, diazepam 1 mg/kg twice daily alone or diazepam and restraint on GDs 12 to 14	The offspring of rats exposed to restraint stress alone were significantly impaired on a number of developmental measures. However, the offspring of animals in the diazepam or diazepam plus restraint group, exhibited a normal rate of development and learning
Jackson et al.[53]	Pregnant Long Evans rats were treated with clorazepate 32 mg/kg and the offspring assessed for neurobehavioural development	A neurological assessment of offspring revealed no significant effects. However, behavioural changes were evident. The offspring of control-treated animals exhibited superior maze learning behaviour than the offspring of drug-exposed animals
Kellogg et al.[58]	Pregnant rats were exposed to diazepam in the third week of gestation	Reported an absence of the locomotor activity burst evident in exposed offspring between postnatal day 14-16. There was also a lack of the acoustic startle response
Alleva et al.[50]	Treated mice on GDs 12 to 16 with oxazepam 0, 5, 15 or 50 mg/kg	Results revealed a dose-dependent retardation of postnatal development of several responses such as righting reflex, bar holding, limb placing and auditory startle, with maximum changes evident in the offspring in the first 2 weeks of postnatal development. A reduction in locomotor activity was evident in the animals in the higher drug group at 60 days postnatal development
Latinien et al.[59]	Pregnant rats were exposed rats to diazepam 10 mg/kg, phenytoin 50 mg/kg or tofizopam 50 mg/kg twice daily between GDs 7 to 21	No drug effects evident on litter size or righting reflex, cliff avoidance, rotarod or passive avoidance in the offspring. There was a lack of the activity burst in the offspring of diazepam-treated animals
Livezey et al.[54]	Rats were given diazepam 5 mg/kg on GDs 15 to 16 and diazepam 7.5 mg/kg on GDs 17 to 18. Offspring were tested in the radial maze at 6 months old	Offspring showed behavioural abnormalities such as increased total immobility, suppressed eating and increased defecation. They also exhibited a longer latency to onset of exploratory behaviour
Cagiano et al.[51]	Rats received a single daily injection of diazepam 0.1 and 1 mg/kg over GDs 14 to 20	A significant decrease in locomotor activity was evident in the offspring of diazepam-treated animals at the end of the second postnatal week. In addition, alterations in the sexual behaviour of these animals were also evident
Gruen et al.[60]	Assessed the effect of perinatal exposure of rats to diazepam	Locomotor activity of the animals was significantly decreased at 90 days of age. Alterations in mesolimbic dopamine turnover was also evident
Pankaj & Brain[61]	Animals were exposed to the benzodiazepine inverse agonists, DMCM and FG 7142 during pregnancy	DMCM retarded and augmented early development depending on the dose used. FG 7142 suppressed later development. When adult social behaviour was assessed, DMCM treatment in male rats produced an increase in threat behaviour

Table II. Contd

Reference	Method	Results
Pankaj & Brain[63]	Animals were exposed *in utero* to chlordiazepoxide or midazolam	Early development of offspring was generally retarded as a result of treatment. An increase in anxiety was observed in male rats and a decrease in female rats. Midazolam was more potent at producing these effects than chlordiazepoxide
Pankaj & Brain[64]	Examined the effect of prenatal exposure to the benzodiazepine antagonist flumazenil and CGS 8216	Early development was facilitated by treatment with RO 15-1788, while CGS 8216 suppressed later development. Altered social behaviour was evident in the animals, with increased threat and attack behaviour evident in male rats treated with both drugs. Female rats showed alterations in digging and defensive/submissive behaviour
Kurshingal et al.[65]	Alderley Park mice were injected with chlordiazepoxide 10 mg/kg and 30 mg/kg during the last 9-10 days of gestation	Postnatal growth of offspring was retarded with alterations in righting reflex, cliff avoidance reflex, rooting behaviour and altered ultrasonic calling
Jaiswal & Bhattacharya[55]	Assessed the effect of undernutrition, stress and diazepam 0.5 mg/kg on learning and retention in young rats. Diazepam was administered on GDs 13 to 20	Undernutrition induced significant learning and retention deficits in the offspring. Pups who were exposed to diazepam treatment alone also exhibited deficits in learning and retention of a discrimination task. However, animals who were undernourished and exposed to diazepam exhibited less cognitive dysfunction
Singh et al.[62]	Pregnant rats were exposed to diazepam 10 mg/kg from GD 13 to 20	A significant decrease in ambulation, grooming, scratching and licking behaviour in the offspring of exposed animals in the open field was evident, while rearing and defecation scores remained unchanged. Significant reductions in exploratory behaviour in the tunnel board and zero maze was evident as well as alterations in social behaviour

DMCM = 6,7-dimethoxy-4-ethyl-beta carboline-3-carboxylate; **GD** = gestational day.

due to other factors such as a family history of cleft, was not found. However, in this study the control group consisted of children exposed to diazepam born with malformations other than cleft lip and cleft palate. Therefore, it has been suggested that without the inclusion of mothers who used diazepam who gave birth to healthy babies the best conclusion that can come from this study is that diazepam is not associated with a greater risk of cleft lip or cleft palate than it is for other anomalies.[76] Similar findings were reported by Hartz et al.,[73] who found no evidence of teratogenic effects for either meprobamate or chlordiazepoxide, taken at any time during pregnancy. In addition, they found no evidence that the drugs were related to either stillbirth or neonatal, infant or childhood mortality. However, due to the small sample size the authors concluded that teratogenicity could not be completely ruled out, but it was extremely unlikely.

It has been suggested, however, that although most children who are exposed *in utero* to benzodiazepines are healthy at birth, exposure late in the third trimester or at delivery, may be associated with an increased risk for the floppy infant syndrome or marked neonatal withdrawal symptoms.[77]

4.4 Human Behavioural Toxicity

Although there is some evidence highlighting teratogenic effects after benzodiazepine exposure, very few studies in this area have focused on the development of behavioural toxicity (see table IV). Two studies that have focused on this area failed to find any long term detrimental effects of diazepam exposure on postnatal development.[77,79]

However, Viggedal et al.[80] found that prenatal exposure to benzodiazepines caused a general delay in mental development up to 18 months of age. McElhatton,[77] reported that in approximately 550 children, who were followed up to 4 years of age, prenatal benzodiazepine exposure was not associated with adverse effects on neurobehavioural development or IQ. Most of the children who were slower to develop in the first year had developed normally by 4 years of age.[77] What effect this slowing of development may have had on emo-

tional development or the mother-child relationship was not addressed.

5. Antidepressant Treatment and Pregnancy

5.1 Animal Toxicity and Teratogenicity

Fetal toxicity following prenatal antidepressant exposure in animals, such as increased offspring/neonatal mortality rates,[81,82] reduced litter sizes at birth,[81] as well as decreased birthweight and growth rate,[82] have been reported for many classes of antidepressant drugs (table V). Two of the major classes of antidepressants, the TCAs and the SSRIs have been studied for their effects during pregnancy.

5.1.1 Tricyclic Antidepressants (TCAs)

Numerous fetal abnormalities associated with TCAs have been noted.[83,86,89] Guram et al.,[87] reported malformations such as cranioschisis, lower body atrophy and external liver in hamsters exposed *in utero* to amitriptyline and imipramine, while Beyer et al.,[90] reported bent tail and encephalocele in animals exposed *in utero* to amitriptyline alone, and cranial malformations, open eye, bent tail, abnormal lung and urogenital abnormalities in animals exposed *in utero* to a combination of amitriptyline and chlordiazepoxide (table V).

In contrast to the above reports, other researchers have found no anomalies in animals exposed *in utero* to imipramine.[84-86] Studies carried out by Hendrickx[91] found no teratogenic effects in monkeys both acutely and chronically exposed to imipramine while *in utero*.

5.1.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

Very limited animal data are available on the effect of prenatal exposure to SSRIs on the developing fetus. One study that addressed this issue reported that prenatal fluoxetine exposure was associated with a statistically significant increase in skin haematomas in the offspring.[88] However, more studies are needed before any conclusive findings regarding the potential teratogenic effects of the SSRIs in animals can be determined.

5.2 Animal Behavioural Toxicity

5.2.1 TCAs

The effects of prenatal antidepressant exposure on postnatal development in animals have also been investigated (see table VI). Deficits in learning behaviour have been reported to occur following prenatal exposure to TCAs.[96] In a series of

Table III. Effect of benzodiazepine exposure on fetal toxicity and teratogenicity – human data

Reference	Method	Results
Saxen & Saxen[66]	Used data from a Finnish register to carry out a retrospective study of 599 women with children with oral clefts and cleft palate	No association was found between the incidence of oral clefts and cleft palate and exposure to diazepam during the first trimester of pregnancy
Safra & Oakley[67]	Study of 278 women who had children with malformations	Children exposed to diazepam in the first trimester of pregnancy had a 4-fold increase in cleft lip or cleft palate
Aarskog[68]	A retrospective study of 130 mothers with children with cleft lip or cleft palate	Results revealed that 6.3% of mothers whose children were born with oral clefts were exposed to diazepam in the first trimester compared with 1.1% of mothers exposed to diazepam whose children did not have oral clefts
Crombie et al.[69]	Assessed the effect of exposure to meprobamate and chlordiazepoxide during pregnancy	Teratogenic effects were found for meprobamate but not for chlordiazepoxide
Patel & Patel[70]	Case report of a mother who had taken chlorazepate during the first trimester pregnancy	The baby was born with malformations of the abdomen, feet and toes. Postmortem examination after death revealed abnormalities of the lung, heart, gastrointestinal tract and the kidney
Laegreid et al.[71]	Study of 36 women exposed to benzodiazepines throughout pregnancy	The authors reported the development of embryofetopathy, dysmorphism and central nervous system dysfunction among these children

Table IV. Effect of benzodiazepine exposure on behavioural fetal toxicity – human data

Reference	Method	Results
Hartz et al.[73]	Studied the effect of *in utero* exposure to meprobamate or chlordiazepoxide. A total 1870 children exposed to either of the drugs *in utero* were compared with control individuals who were not exposed	Drug exposure was not associated with an increase in malformations, or increased incidence of stillbirth. In addition, no alterations were evident in postnatal development or IQ scores at 4 years of age
Delaney[74]	Assessed clinical case reports of pregnant women who received intravenous diazepam during anaesthesia	No malformations were found after *in utero* exposure to a single dose
Rosenberg et al.[75]	Investigated the incidence of drug exposure among 445 children born with cleft lip with or without cleft palate and 166 born with cleft palate without cleft lip. These children were then compared with control individuals without these abnormalities	Reported that exposure to diazepam in the first trimester of pregnancy was not associated with an increase in the birth of children with oral cleft
Shiono & Mills[78]	Assessed the effect of diazepam exposure in the first trimester of pregnancy and the incidence of oral clefts	No associated was found between diazepam exposure in the first trimester and the development of oral clefts
Milkovich & Van den Berg[72]	Exposure to meprobamate and chlordiazepoxide	Found that meprobamate and possible chlordiazepoxide may be teratogenic when taken during the first 6 weeks of gestation
Stika et al.[79]	Assessed the effect of exposure to benzodiazepines or antipsychotics during the second half of pregnancy, on the subsequent behavioural development of the infants. The study involved 68 children with possible antipsychotic exposure and 55 control children and 15 children possibly exposed to diazepam and 7 control children	No significant differences between the groups were found
Viggedal et al.[80]	Prospective study assessing the effect of prenatal benzodiazepine exposure on mental development in late infancy. The study involved 17 infants whose mothers had taken benzodiazepines during pregnancy and 29 control infants	A general delay in mental development up to 18 months was found

studies in the 1970s, Coyle and Singer[92] reported detrimental effects of prenatal antidepressant exposure on the subsequent development of the offspring. Exposed animals reared in an enriched environment were shown to be behaviourally unresponsive and spent significantly less time interacting with each other than unexposed animals reared in the same environment. When maze learning was assessed, again exposed animals reared in the enriched environment were significantly impaired compared to unexposed animals reared in the same environment. However in a later study, Coyle and Singer,[93] found no effect of prenatal imipramine exposure on performance during a spontaneous alternation task or swimming maze test.

Alterations in emotional and exploratory behaviour of animals exposed prenatally to antidepressants has also been recorded.[96,97] However, MAOIs were more potent in inducing these effects than TCAs.[96] Coyle[98] treated female rats with imipramine 5 mg/kg prior to, and up to, gestation day 19. Decreased exploratory responses were evident in the offspring of these animals. Similarly, Roderiquez-Echandia and Broitman,[95] reported behavioural deficits in the offspring of animals treated with clomipramine during pregnancy with male offspring showing a significant increase in digging and grooming, decreased exploratory behaviour and decreased social interactions.

Despite these findings, an anxious behaviour was observed in animals exposed to clomipramine *in utero* and reared in an enriched environment, when tested in the social interaction test, by File and Tucker.[94] Although decreased rearing and ex-

ploration were evident in this study, this reflected a faster habituation to the test environment.[94]

5.2.2 SSRIs

Although behavioural abnormalities have been reported to occur following prenatal exposure to MAOIs and TCAs, the effect of exposure to the SSRIs in animals has received little attention. One study that addressed the effect of prenatal exposure in rats to the SSRI, fluoxetine, found no effect on a series of behaviours including locomotor activity, spontaneous alternation, passive avoidance or water maze performance. The authors concluded that fluoxetine was not developmentally neurotoxic in the rat.[81]

5.3 Human Teratogenicity

The effect of prenatal antidepressant exposure on human fetal development has also been assessed. Most of the studies in this area have focused on exposure to TCAs and the SSRIs (see table VII).

5.3.1 TCAs

Although there have been reports of fetal abnormalities in humans associated with TCA exposure *in utero*,[101-103,105,106,111] many later studies have failed to find such an association.[107,112]

Fetal abnormalities such as anopthalmia,[106] defective abdominal muscles and gut,[102] cardiac anomalies[111] as well as central nervous system and bone abnormalities[101,105] have been reported to occur following prenatal exposure to TCAs. In

Table V. Effect of prenatal antidepressant exposure on fetal toxicity – animal data

References	Method	Results
Robson & Sullivan[83]	Pregnant rabbits were exposed to imipramine 30 mg/kg	Fetal malformations were reported in some instances
Orberholzer[84]	Pregnant rabbits and rats were exposed to imipramine 25 to 50 mg/kg	Although toxic effects were evident in the mothers at higher doses, no anomalies were observed in the offspring
Jelinek et al.[85]	Rats were exposed to imipramine and amitriptyline during pregnancy	No malformations were observed
Aeppli[86]	Imipramine, desmethylimipramine and 2-OH-imipramine were administered to pregnant rats. Rabbits were treated with 2-OH-imipramine 40 mg/kg orally	No anomalies were observed in the offspring of rats. In the rabbits, skeletal anomalies were observed in the offspring
Gurum et al.[87]	Animals were given a combination of amitriptyline and chlordiazepoxide on GD 8	A number of fetal abnormalities were evident including exencephaly and encephalocoele. A dose-response relationship was found, with combinations in the range of amitriptyline/chlordiazepoxide 33/13-83/33 mg/kg producing 7-92% of fetal anomalies. The combination of the 2 drugs was more teratogenic than either drug alone
Simpkins et al.[82]	Rats received injections of doxepin daily, either in the first trimester (GDs 1 to 7), the second trimester (GDs 8 to 14) or the third trimester (GDs 15 to 21) of pregnancy. Imipramine was administered during the third trimester only	An increase in infant mortality rate was evident in animals exposed to doxepin in the first and second trimester. Imipramine exposure in the third trimester increased mortality rate, reduced birthweight and growth rate. Exposure to either of these drugs in the third trimester enhanced the responsiveness of the -adrenergic system in the aorta. No effect of these antidepressants was observed on blood pressure
Stanford & Patton[88]	Sprague-Dawley rats received fluoxetine 5.62 mg/kg by oral gavage from GD 7 until birth	A significantly higher incidence of skin haematomas was evident in the offspring of fluoxetine-exposed animals as compared with control animals
Vorhees et al.[81]	Sprague-Dawley rats were treated with fluoxetine 1, 5 or 12 mg/kg on GDs 7 to 20. Animals were tested for neurobehavioural development prior to weaning, as juveniles and as adults	Maternal weight loss, reduced litter size and increased neonatal morality were evident at the highest doses of fluoxetine. However, fluoxetine administration had no effect on behavioural development of exposed offspring

GD = gestational day.

Table VI. Effect of prenatal tricyclic antidepressant (TCA) exposure behavioural development – animal data

Reference	Method	Results
Coyle & Singer[92]	Rats were treated with either saline or imipramine 5 mg/kg prior to mating until parturition. The offspring of these animals were then raised in either an enriched or deprived environment. Behavioural testing of the offspring in the enriched environment was carried out at 25-27 and 80-83 days of age	The offspring did not display the histological changes normally evident in animals reared in an enriched environment. In addition, the behavioural development of these animals was altered as they spent significantly less time than control animals interacting with each other and the environment
Coyle & Singer[93]	Rats were administered imipramine 5 mg/kg for 14-21 days prior to mating, conception or GD 19	Significant differences in bodyweight were evident between the offspring of imipramine-treated animals and the offspring of control animals at 21 days of age. Decreased exploratory behaviour was evident in the offspring of imipramine-treated animals when tested in the open field; however, no differences were evident between the groups on performance on a spontaneous alternation task or the swimming maze
File & Tucker[94]	Pregnant rats were treated with clomipramine on GDs 8 to 21. The offspring were reared in an enriched environment after weaning and their behavioural development assessed in adolescence and adulthood	Decreased rearing and less exploration was evident in the offspring of clomipramine-treated animals reportedly due to a faster habituation response to the novel environment. In addition, anxious behaviour was evident in these animals in the social interaction test
Roderiquez-Enchandia & Broitman[95]	The effect of clomipramine exposure either during pregnancy, lactation or throughout pregnancy and lactation on the developing fetus and subsequent behavioural development was assessed	Clomipramine treatment during pregnancy did not have any teratogenic effects and had no affect on litter size, birthweight or neonatal mortality. Some behavioural changes were evident in the offspring at 2 months of age, with an increase in grooming and digging behaviour and decreased social behaviour in male offspring. Female animals appeared to be more resistant to prenatal clomipramine exposure. Clomipramine treatment during lactation had minor effects on behaviour, while clomipramine exposure through pregnancy and lactation enhanced the effects seen with clomipramine exposure during pregnancy
Drago et al.[96]	Rats were administered either imipramine, desipramine, clomipramine, iproniazid or isocarboxazid either on GD 15 or from GD 10 to delivery or neonatally from day 1-5 of age	No changes in behaviour were evident after acute antidepressant exposure. However, subchronic antidepressant administration affected behavioural development with alterations evident in open field behaviour as well as alterations in the acquisition of an active avoidance response. In addition, an increase in the number of pups showing neonatal reflexes was also evident in this group. MAOIs appeared to be more potent at producing these effects than TCAs. Alterations in active avoidance response were also evident in the animals who were exposed to the antidepressants neonatally. In this group of animals, only isocarboxazid produced deficits in open field behaviour

GD = gestation day; **MAOI** = monoamine oxidase inhibitor.

contrast, reports failed to find any association[100,104,113] and in many cases where limb abnormalities occurred, the mothers were not exposed to antidepressant drugs.[99]

The evidence for an effect of prenatal TCA exposure on the developing infant is far from clear. Varying sample sizes, the concomitant use of other medication, as well as the paucity of information regarding other potential factors affecting development make interpretation of these findings difficult.

5.3.2 SSRIs

Pastuszak et al.,[108] reported that fluoxetine exposure during the first trimester of pregnancy in 128 women was not associated with an increase in fetal malformations. However, an increased risk of miscarriage was evident in this group when compared with control individuals, but the risk did not differ from that in women treated with a TCA. In addition, Chambers et al.,[109] reported that while prenatal fluoxetine exposure in 228 women was not associated with an increase in major fetal ab-

normalities, there was an increase in the incidence of 3 or more minor anomalies in these infants. They also found that infants exposed to fluoxetine in the third trimester of pregnancy had higher rates of premature delivery, admission to special care nurseries, respiratory difficulty, cyanosis on feeding and jitteriness than infants exposed to fluoxetine in the first or second trimester only. Kulin et al.,[110] however, reported that use of the SSRIs sertraline, fluoxetine and paroxetine during pregnancy was not associated with increased teratogenicity if used at their recommended dosages.

5.4 Human Behavioural Toxicity

Little research has been conducted into the effects of either prenatal TCA or SSRI exposure on postnatal behavioural development (see table VIII). Nulman et al.,[112] assessed the effect of prenatal exposure to fluoxetine or a TCA on postnatal development. Mean global IQ scores for children

Table VII. Effect of prenatal tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI) exposure fetal toxicity – human data

Reference	Method	Results
Banister et al.[99]	Retrospective study looking at the incidence of drug exposure in 168 children born with limb anomalies	Results revealed that only 25 out of 168 children were exposed to TCAs
Crombie et al.[100]	Retrospective study assessing the effect of exposure to imipramine or amitriptyline *in utero*	No anomalies were reported in the children exposed to imipramine and there was 1 case of a child exposed to amitriptyline who was born with swollen hands and feet. However, the child was healthy at 2 years of age
Freeman[101]	Case report of a woman exposed to amitriptyline in the first trimester of pregnancy	Abnormalities were evident in the infant with absent left fibula, hypoplastic tibia and foot reported
Kuensberg & Knox[102]	Assessed the effect of prenatal exposure to either imipramine or amitriptyline in 17 women	Reported abnormal muscle and gut in 1 child exposed to imipramine, 1 case of abortion of a child with hypospadias who was exposed prenatally to imipramine
McBride[103]	Case reports of 3 women who were exposed to imipramine during pregnancy	Limb abnormalities were reported
Rachelefsky et al.[104]	A retrospective study of 101 infants born with limb abnormalities	The children were not exposed to TCAs
Idanpaan-Heikkila & Saxen[105]	Retrospective study assessing the incidence of drug exposure among 2784 children with birth defects	Five infants with malformations were exposed to TCAs, 4 had CNS anomalies and 1 had multiple bone anomalies
Golden & Perman[106]	Case report of a women who was exposed to multiple drugs during pregnancy, including amitriptyline and pentobarbitol (phenobarbitone)	The infant was born with bilateral clinical anopthalmia
Misri & Sivertz[107]	Assessed the effect of TCA exposure *in utero* on the developing fetus. They examined women who became pregnant while taking TCAs, women who were prescribed TCAs during pregnancy, women prescribed TCAs during lactation and women who were depressed during lactation but who refused to take medication	No fetal abnormalities were reported in the drug-exposed infants. In addition, there was no change in the incidence of complications during labour and delivery, and only short term withdrawal symptoms were evident in the neonates
Pastuszak et al.[108]	Compared the effect of fluoxetine exposure (128 women), with TCA exposure and control individuals	No association was found between fetal abnormalities and drug exposure. However, women treated with fluoxetine and TCAs were shown to have an increased risk of miscarriage than women in the control group
Chambers et al.[109]	Prospective study which examined the effect of fluoxetine exposure *in utero* on the developing fetus. 228 women were taking fluoxetine and there were 254 control women	No significant differences in the rate of spontaneous abortion was evident between the women treated with fluoxetine and the control group of women. Although the rate of major structural anomalies was not different between the groups, the incidence of minor anomalies was shown to be increased in the fluoxetine group. In addition, fluoxetine exposure in the third trimester was associated with an increased incidence of premature delivery, admission to special care nurseries, respiratory problems and jitteriness
Kulin et al.[110]	Prospective study to assess fetal safety and risk of fluvoxamine, paroxetine and sertraline. 267 women were exposed to SSRIs and there were 267 controls	The SSRIs fluvoxamine, paroxetine and sertraline do not appear to increase the teratogenic risk when used at their recommended dosages

Table VIII. Effect of prenatal antidepressant exposure on behavioural development – human data

Reference	Method	Results
Nulman et al.[112]	Assessed the effect of prenatal exposure to either a TCA (80 children) or fluoxetine (55 children) on postnatal development of children; there were 84 control children. The behavioural development of the children was assessed at 16 and 85 months of age	Prenatal exposure to either drug had no effect on global IQ, language development, or any detrimental effect on temperament, distractibility or behavioural development
Buist & Janson[114]	Assessed the effect dothiepin exposure in breast milk on the developing infant as compared with control individuals. Women and their children were assessed at 3-5 years post partum. The study involved 30 women with depression and 36 women without depression	No significant differences were evident between the groups except on marital conflict and child behaviour. Cognitive performance was not significantly different between the groups

TCA = tricyclic antidepressant.

exposed to TCAs were 118 ± 17, 117 ± 17 for those who were exposed to fluoxetine, and 114 ± 14 in the control group. The language scores were similar in all 3 groups. The results were similar for children exposed to an antidepressant in the first trimester and those exposed to an antidepressant throughout pregnancy. No significant differences in temperament, mood, distractibility, activity level, arousability or behavioural problems between the 3 groups of children were found. The authors concluded that exposure to a TCA or fluoxetine *in utero* does not affect global IQ, language development or behavioural development in preschool children.[112]

In another study, Buist and Janson,[114] reported no negative association between exposure to dothiepin via breast milk and cognitive development in children assessed at 3 to 5 years post partum.

6. Conclusion

It seems clear that the issue of the safety of psychotropic drugs during pregnancy is far from resolved. Results of studies looking at this issue are not straightforward and at times are contradictory. Whilst some of the findings in animal studies are concerning, they cannot be directly extrapolated to humans. Human studies are complicated by varying sample sizes, multiple drug/toxin exposure, and in the case of the follow-up studies in particular, multiple other factors affecting child development.

In addition, methodological differences between the studies further complicate findings. Many of the studies are case reports and as such, are affected by limited sample sizes. Similarly, retrospective studies may be influenced by underreporting of drug consumption by the mothers.

Although, if possible, nonpharmacological treatments, such as cognitive behavioural therapy, should be the used to treat women with pre-existing psychiatric conditions during pregnancy, this is often not possible. Women frequently require medication for the treatment of pre-existing disorders or new onset disorders, and there is a need therefore to balance the risks of withholding medication against the risk to both the mother and the child of using drugs during pregnancy. When medication is required, women should be prescribed the lowest dosage of drug for the shortest length of time[35] with the aim of minimising any potential negative effects. Keeping dosages low close to the time of delivery may also be a benefit in minimising withdrawal and adverse effects in the newborn.

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