

Benzodiazepine use in Pregnancy

Some dangers of benzodiazepine use in pregnancy

“Exposure of our most valuable resource, our children, to harmful developmental effects of drugs is a problem of staggering proportion.” *Huestis M.*¹

The dangers to newborn babies exposed to drugs such as alcohol, illicit drugs and tobacco in pregnancy are well known but the risks of prescribed drugs are rarely examined. In 1978, the Australian National Drug Information Service stated that benzodiazepines (BZs) were contraindicated during pregnancy.²

In 1977, the dangers of BZs during pregnancy were highlighted in a letter to *The Lancet* by paediatrician Dr Nigel Speight.²⁰

A warning by the Committee on Safety of Medicines was issued regarding the dangers of BZs in pregnancy in a reminder in 1997.⁸

BZs are classified by the US Food and Drug Administration (FDA), as pregnancy category 'D',^{3,4} which should not normally be taken during pregnancy and category 'X',⁵ which should never be taken during pregnancy (opiates are category 'B' or 'C'). *See FDA categories below.

Incidence

Worldwide, an estimated 85% of all psychotropic medicines prescribed to pregnant women are for BZs.⁹ The incidence of BZ use during pregnancy is unclear and figures varying from 1-3%,¹⁰ to 40%¹¹ have been suggested. These figures do not include women who misuse BZs, 90% of whom are of childbearing age¹².

BZs were detected in 18% of infants born between October and November 2000 at a Glasgow maternity hospital¹³

Prescribing

“We noted a high rate of prescribing of benzodiazepines to pregnant women in spite of documented evidence that this may lead to the so-called “floppy baby syndrome” of neonatal drowsiness, hypotonia and withdrawal symptoms” *O’Shaughnessy P., IMJ, 1993*¹⁴

It is a legal requirement that all prescribed medicines in the UK are dispensed with an attached Patient information leaflet.¹⁵ Information leaflets for BZs state that they should not be taken during pregnancy, but not all women receive this warning. Although illegal, some prescriptions are currently issued without leaflets.¹⁶

The Committee on Safety of Medicines issued a reminder warning of the dangers of BZ use in pregnancy in 1997,⁸ but prescribing of hypnotics and anxiolytics to women of childbearing age rose between 1994 and 1998 (fig. 1).¹⁷

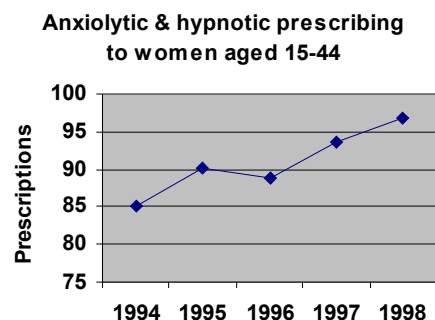


Fig. 1. Anxiolytic & hypnotic prescribing to women aged 15-44 in the UK, 1994-1998 (adapted), source, General Practitioner Database.⁶²

Short-term problems

Problems at birth

Babies exposed to BZs during pregnancy are at risk of the following:

45. **Low birth weight.** ¹⁸
46. **Breathing difficulties.** ^{19,20}
47. **“Floppy” muscles.** ¹⁹
48. **Unstable body temperature.** ¹⁹
49. **Alteration in heart rate/function.** ^{6,19.}
50. **Altered EEG measurements.** ²¹
51. **Withdrawal syndrome (can be protracted) with irritability, convulsions etc.** ^{19,22.}

Prenatal BZ exposure can cause toxicity and/or withdrawal effects at birth. Affected babies may need months of treatment, sometimes in special care, ^{23,24,25.} whereas the adverse effects of prenatal opiate exposure lasts 2-4 weeks. ²⁵

Flumazenil, a BZ antagonist ('antidote') that can reverse many effects of BZs (licensed for use in surgical procedures and overdose), has been used in emergencies (outside of license) in some BZ-exposed neonates, successfully reversing most of the above adverse effects. ^{26,27,28,29.}

Breathing difficulties

“The baby might have died on a postnatal ward of an apnoeic episode had he not been admitted to a special care nursery.” *The Lancet*, 1977 ²⁰

BZs are a risk factor in cot death as they can interfere with breathing regulation ^{19,20.} and the drug can remain active in the baby's system for long periods. ^{6,11.}

No specific investigation appears to have been done into prenatal BZ use and cot death. ³⁰

Instances of cot death in BZ-exposed infants have been reported ^{31,32} and in one study the use of nitrazepam has been implicated in sudden unexpected deaths in children. ^{33.}

Long-term problems

“ Diazepam should be avoided in pregnant or lactating animals... in humans, it has been shown to be teratogenic when used during the first trimester of pregnancy. Diazepam crosses the placenta and is present in milk.” *Veterinary advice*, 2001 ^{44.}

Malformations

Conflicting reports of the incidence of cleft palate and other malformations have continued to emerge since the 1970s; the results remain unclear. A recent meta-analysis (2000) of 13 studies showed no increased risk of BZ-induced malformations from cohort studies and slight increased risk from case-controlled studies. ^{34.}

Developmental effects

Animal studies show that BZs can interfere with foetal development including neurodevelopment, ^{45, 35} and development of the immune system. ^{36,37.}

Current human research ^{38,39} reflects many animal findings, as do the growing anecdotal reports.

An informal study amongst self-reported parents of 63 BZ-exposed children ⁴⁰ revealed high rates of neonatal and later developmental problems; e.g. 30% needed treatment in special care at birth and 31% developed learning difficulties. Unexposed siblings were reported to be unaffected, indicating that further research is needed.

Consequences of parental benzodiazepine use

Cognitive and other health problems due to parental BZ use can impair parenting skills ⁴¹ with negative consequences for the children and the family.

Research shows a direct link between parental BZ use (mainly maternal), and subsequent BZ use/misuse in their adolescent children. ^{42,43.}

*** Category X benzodiazepines include: Flurazepam, Estazolam, Temazepam, Quazepam Triazolam**

Definition of FDA pregnancy categories: The FDA-assigned pregnancy categories as used in the Drug Formulary:

FDA Pregnancy Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

FDA Pregnancy Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

FDA Pregnancy Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

FDA Pregnancy Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

FDA Pregnancy Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnancy.

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