Medicines Adverse Reactions Committee

Meeting date	12/09/2024	Agenda item	3.2.2
Title	**Use of benzodiazepines for non-epilepsy indications during pregnancy and the risk of miscarriage**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	**PHARMAC funding**
diazepam	Arrow - Diazepam tablet	Teva	Y
	DBL Diazepam injection	Pfizer	Y
lorazepam	Ativan tablet	Pharmacy Retailing	Y
midazolam	Midazolam solution of injection	Pfizer	Y
		Viatris	
		Baxter	Y
temazepam	Normison tablet	Pharmacy Retailing	Y
Previous MARC meetings	Not previously discussed		
International action	None		
Prescriber Update	None		
Classification	Prescription medicine		
Usage data (NZ)	During 2012-2021, the use of these benzodiazepines during pregnancy was about 1% of all pregnancies		
Advice sought	**The Committee is asked to advise:** • on the strength of the evidence for an association between the benzodiazepines included in this review and the risk of miscarriage.		

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1 PURPOSE

An article on the use of benzodiazepines during pregnancy and risk of miscarriage was recently published in *JAMA Psychiatry* by Meng et al [1]. This was a nationwide, population-based, case-time-control study conducted in Taiwan. The methodology used in the study was difficult to understand, which prompted Medsafe to seek expert advice from the Committee.

Benzodiazepines have been available in NZ for many years. For example, Valium (diazepam) was first approved in 1969. Benzodiazepines are used in the treatment of severe anxiety, severe insomnia, as a pre-medicant, and in epilepsy.

This review focuses on the use of benzodiazepines during pregnancy for the treatment of non-epilepsy indications and the safety concern is miscarriage.

2 BACKGROUND

2.1 Benzodiazepines

The following benzodiazepines are included in this review as there are NZ approved and marketed products with non-epilepsy indications:

- diazepam tablets and solution for injection
- lorazepam tablets
- midazolam solution for injection
- temazepam tablets.

These benzodiazepines are excluded from this review:

- indicated in epilepsy only: oral clobazam, oral clonazepam and diazepam rectal tubes
- NZ approval lapsed: alprazolam tablets, bromazepam tablets, chlordiazepoxide capsules, flurazepam capsules, oxazepam tablets and nitrazepam tablets.

Benzodiazepines are Class C5 controlled drugs, meaning the maximum prescription duration is 3 months (90 days) dispensed in monthly lots [2].

2.1.1 Indications

Benzodiazepines facilitate the synaptic actions of gamma aminobutyric acid (GABA). They have anxiolytic and hypnotic properties and are used in a variety of non-epilepsy indications. As shown in Table 1, these include severe anxiety, severe insomnia, and as a pre-medicant.

Table 1: Non-epilepsy indications of benzodiazepines

Medicine	Indications
Diazepam (Arrow - Diazepam tablets)	Adults • Short-term (2 to 4 weeks) symptomatic treatment of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness. • Short-term (2 to 4 weeks) treatment of conditions where anxiety may be a precipitating or aggravating factor (eg, tension headaches, migraine attacks). • Symptomatic treatment of acute alcohol withdrawal. • Muscle spasm. As an adjunct to the control of muscle spasm in tetanus. • May be useful in the management of cerebral spasticity in selected cases. • Premedication Children • Night terrors and somnambulism. • May be useful in controlling tension and irritability in cerebral spasticity in selected cases. • As an adjunct to the control of muscle spasm in tetanus. • Premedication.
Diazepam (DBL Diazepam solution for injection)	• Tension and anxiety states. • Preoperative medication. • Skeletal muscle spasm and motor unrest. • Cerebral palsy. • Athetosis. • Stiff-man syndrome. • Tetanus and acute agitation due to alcohol withdrawal.
Lorazepam (Ativan tablets)	Useful in the therapy of most disorders in which anxiety is a major component. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. • Treatment of moderate to severe anxiety • Treatment of insomnia associated with anxiety • Pre-medication before surgery.
Midazolam solution for injection (Pfizer, Viatris, Baxter)	• Premedication before induction of anaesthesia. • Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia. • Long-term sedation in intensive care units. • Induction and maintenance of anaesthesia. As an induction agent in inhalational anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia. • Ataralgesia in combination with ketamine in children.
Temazepam (Normison tablets)	• As a hypnotic or night-time sedative. As a hypnotic, Normison is indicated for severe or disabling insomnia characterised by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening. • As a premedicant taken 30-60 minutes prior to surgical or other procedures.

Source: NZ medicine data sheets (accessed 12 August 2024)

2.1.2 Usage

The Qlik Pharmaceutical dispensing in pregnancy app combines data from the National Maternity Collection (MAT), Pharmaceutical Collection (PHARMS) and National Minimum Dataset (NMDS). This was used to estimate how widely benzodiazepines are used during pregnancy. The app includes data on Pharmac-funded prescription medicines dispensed from a community pharmacy to women during pregnancy from 2012 to 2021.

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Source: National Maternity Collection, Pharmaceutical Collection, National Minimum Dataset (data extracted via Qlik Pharmaceutical dispensing in pregnancy app 14 August 2024)

[redacted]

In a 2021 US study on opioid and benzodiazepine prescribing patterns [3], the prevalence of benzodiazepine dispensing during pregnancy was found to have increased between 2007 and 2015 (1.3% to 2.9%). The prevalence of benzodiazepine dispensing was found to have increased over time (2007 vs 2015) during the pre-conception period (2.3% vs 3.8%), first trimester (1.1% vs 2.1%), and second trimester (0.3% vs 0.5%).

Source: National Maternity Collection, Pharmaceutical Collection, National Minimum Dataset (data extracted via Qlik pharmaceutical dispensing in pregnancy app 14 August 2024)

2.1.3 NZF guidance [4-6]

As a hypnotic

Benzodiazepines used as hypnotics include diazepam and temazepam. Diazepam has a longer duration of action and may result in residual effects the next day. Repeated doses of diazepam tend to be cumulative. Temazepam has a shorter duration of action and has little to no hangover effect. Withdrawal phenomena are more common with short-acting benzodiazepines.

If insomnia is associated with daytime anxiety, the use of a long-acting benzodiazepine such as diazepam given at night may treat both symptoms.

Benzodiazepines should only be used to treat insomnia when it is severe, disabling or causing the patient extreme distress. Treatment should be limited to a short course and repeat prescriptions should not be provided without clinical review.

As an anxiolytic

Benzodiazepines are indicated for the short-term relief (2 to 4 weeks) of anxiety that is severe, disabling or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term illness. The use of benzodiazepines to treat short-term 'mild' anxiety, stress-related symptoms, unhappiness or minor physical disease is inappropriate.

Benzodiazepine anxiolytics should not be used as sole treatment for chronic anxiety, and they are not appropriate for treating depression or psychosis. In bereavement, psychological adjustment may be inhibited

by benzodiazepines. In children, anxiolytic treatment should be used only to relieve acute anxiety (and related insomnia) caused by fear (eg, before surgery).

As a peri-operative sedative and analgesic

Benzodiazepines are useful as premedication to relieve anxiety, for sedation and amnesia. Oral short-acting benzodiazepines are the most common pre-medicants. Benzodiazepines are also used in intensive care units for sedation, particularly for those receiving assisted ventilation.

Midazolam is the preferred benzodiazepine for premedication and for sedation. It has a fast onset of action and recovery is quicker than for other benzodiazepines.

2.2 Pregnancy and miscarriage

2.2.1 Insomnia during pregnancy

Sleep disturbance increases during the course of pregnancy. The overall prevalence of insomnia symptoms during pregnancy was estimated as 38.2% based on a meta-analysis by Sedov et al (2021) [7]. The prevalence of insomnia symptoms was higher in the third trimester (39.7%) compared to the first (25.3%) and second (27.2%) trimesters.

Although many pregnant women have disturbed sleep, most do not identify it as a disorder because they may be prepared for it or recognise that it is time limited [8]. However, some patients have more severe insomnia or are more severely disturbed by nighttime awakenings or associated daytime dysfunction [8].

There are few data from controlled studies on the treatment of insomnia in pregnancy. Non-pharmacologic therapies are the safest option and are preferred over pharmacotherapy by most patients [9-11]. Several randomised trials support the efficacy of cognitive behavioural therapy for insomnia (CBT-I) in pregnancy [12-16].

OTC sedating antihistamines such as doxylamine or diphenhydramine may be used in patients who desire taking a medicine and have no alternative causes of sleeplessness that can be addressed (eg, restless legs syndrome, gastroesophageal reflux) [8]. Other pharmacologic options, including benzodiazepines, Z-drugs (such as zopiclone) and sedating antidepressants should generally be avoided as potential risks likely outweigh benefits [8].

2.2.2 Anxiety during pregnancy

A meta-analysis from 2017 [17] found the prevalence of self-reported anxiety symptoms to be 18.2% (95% CI 13.6-22.8) during the first trimester. This was similar to the prevalence for a clinical diagnosis of any anxiety disorder during the first trimester which was 18% (95% CI 15-21.1).

Australian government data suggests that anxiety and/or depression is experienced by up to 10% of women during pregnancy [18]. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) best practice statement for mental health care in the perinatal period does not include any information on benzodiazepines.

The UK NICE guidelines [19] state not to offer benzodiazepines to women in pregnancy and the postnatal period except for short-term treatment of severe anxiety and agitation, and to consider gradually stopping benzodiazepines in women who are planning a pregnancy, are pregnant, or considering breastfeeding.

According to Micromedex [20], the American College of Obstetricians and Gynecologists (ACOG) strongly recommends that benzodiazepines be avoided or prescribed sparingly for the treatment of perinatal anxiety. Benzodiazepines are not recommended as first-line pharmacotherapy for the treatment of anxiety disorders. If benzodiazepines are used in the treatment of anxiety, ideally they would serve as a bridge until the expected treatment response is observed with SSRIs, SNRIs, or psychotherapy. Benzodiazepines should only be used as needed for 2 to 4 weeks until a response to first line treatment is observed, followed by a taper of 25-50% per week.

Comments:
There are estimates of prevalence/incidence of insomnia and anxiety during pregnancy. However, the severity is unknown.

2.2.3 Miscarriage [21-23]

Miscarriage (spontaneous abortion, early pregnancy loss) is defined as a pregnancy that ends on its own before 20 weeks gestation. It is fairly common, affecting 1 or 2 in every 10 pregnancies. Most miscarriages (>95%) occur in the first 12 to 14 weeks of pregnancy (ie, during the first trimester). The cause of miscarriage is often not known.

The prevalence of miscarriage is strongly influenced by maternal age (Figure 2). According to a 2019 study [24], 25 to 29-year-olds are at lowest risk of miscarriage (10% risk). Women <20 years of age were found to have a similar risk of miscarriage as women aged 35-39 years (around 16%). The risk of miscarriage is significantly higher in women aged >40 years.

Miscarriage is usually a natural process. There is a complex chain of events from conception through to early pregnancy. Most miscarriages occur because something happened with the development of the baby during or soon after conception. This could be related to a problem with cell development as the baby forms, the mother's health, infection or issues with the development of the placenta.

Figure 2: Risk of miscarriage in first pregnancy, by age

International literature suggests miscarriage can have a lasting effect on mental health, from mental distress to symptoms or diagnoses of post-traumatic stress disorder and anxiety. The association with depression seems less clear, however some evidence indicates a higher risk of suicide and self-harm.

2.3 Data sheets

2.3.1 New Zealand

None of the data sheets include any information on miscarriage. Information on use during early pregnancy is shown in Table 3 (ie, information on use during late pregnancy is not included).

Table 3: Information on early pregnancy in data sheets

Medicine	Early pregnancy information
Diazepam (Arrow - Diazepam tablets)	Section 4.6 (pregnancy) Category C If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant. There are limited amount of data from the use of diazepam in pregnant women. Studies in animals have shown reproductive toxicity.

Diazepam (DBL Diazepam solution for injection)	Section 4.6 (pregnancy) Category C The safety of diazepam for use in human pregnancy has not been established. Diazepam and its metabolites readily cross the placenta. Do not administer diazepam during the first trimester of pregnancy. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Diazepam was found to be teratogenic in mice at intravenous doses of 45 mg/kg or greater and oral doses of 100 mg/kg or greater (both 10-fold the MRHD on a body surface area basis), as well as in hamsters at 280 mg/kg (41-fold the MRHD). The respective no-effect doses were 50 mg/kg (5-fold the MRHD) in mice and 200 mg/kg (30-fold the MRHD) in hamsters. Malformations included exencephaly, cranioschisis, kinking of the spinal cord, and cleft palate with and without cleft lip. Malformations were not observed in rats or rabbits at respective doses of up to 300 and 50 mg/kg/day (greater than 20-fold the MRHD). Delayed development has been reported in offspring from several animal species treated with diazepam during pregnancy or during pregnancy and lactation.
Lorazepam (Ativan tablets)	Section 4.4 (warnings and precautions) Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6). Section 4.6 (pregnancy) Category C. The use of benzodiazepines during the first trimester of pregnancy should almost always be avoided. If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant. Risk summary statement [as shown under section 4.4]
Midazolam solution for injection (Pfizer)	Section 4.6 (pregnancy) Australian Pregnancy Category C Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of fetal development, nor has clinical experience so far yielded any evidence of such an association. However, like any other drug, midazolam should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician. Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

Midazolam solution for injection (Viatris)	Section 4.6 (pregnancy) Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. However insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.
Midazolam solution for injection (Baxter)	Section 4.6 (pregnancy) Category C Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Teratological studies with midazolam in a number of animal studies have not shown association between administration of the drug and disturbances of foetal development, nor has clinical experience so far yielded any evidence of such an association. Midazolam should not be used in the first three months of pregnancy. Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes. Risk summary statement Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.
Temazepam (Normison tablets)	Section 4.4 (warnings and precautions) Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6). Section 4.6 (pregnancy) Category C Temazepam should not be used during pregnancy. The use of benzodiazepines during the first trimester of pregnancy should almost always be avoided. An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant. Risk summary statement Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Source: NZ medicine data sheets (accessed 12 August 2024)

3 SCIENTIFIC INFORMATION

3.1 Published literature

A PubMed search of (benzodiazepine) AND (miscarriage) yielded 56 results. Abstracts were manually reviewed. Relevant articles are summarised below.

3.1.1 Meng et al 2023 – Benzodiazepine use during pregnancy and risk of miscarriage (Annex 1) [1]

This study prompted the review of this topic.

Objective

To quantify the risk of miscarriage associated with benzodiazepine use during pregnancy after controlling for unmeasured confounders and exposure time trends.

Data source

Nationwide, population-based case-time-control study using Taiwan's National Birth Certificate Application (BCA) database 2004-2018 and the National Health Insurance (NHI) database 2002-2019. The NHI database comprises anonymised health insurance claims for visits, procedures and prescriptions for more than 99% of the population in Taiwan. The BCA records all live births and stillbirths with gestational age of >20 weeks or birth weight >500 g. Data in these two databases were linked using patient identification numbers.

Study population

Pregnancies resulting in miscarriage were identified from the NHI database. Pregnant women who had their first prenatal care visit were included and women with records of births in the BCA database and those without a diagnosis of miscarriage were excluded. End of pregnancy was defined as date of miscarriage and the last menstrual period was calculated as the date of the first prenatal care visit minus 56 days.

Pregnancies resulting in live births or stillbirths were identified from the BCA database. End of pregnancy was defined as the birth date of the newborn and the last menstrual period was calculated as the birth date of the newborn minus the number of days of pregnancy.

Case-time-control design

A case-time-control study design was used, which is a within-person comparison. This design comprised 2 self-adjusted analyses: a case-crossover analysis and an exposure time-trend control crossover analysis (Figure 3).

Through case-crossover analysis, time-invariant factors such as underlying disease severity and genetic factors could be automatically controlled by using case individuals as their own controls. However, the case-crossover design estimates odds ratios for associations obtained solely from the exposure of case individuals at different time points, which may potentially reflect changes in drug use associated with the event occurrence.

Therefore, an exposure time-trend control crossover analysis was incorporated to adjust for background time trends. This adjusts for time invariant confounders and exposure time-trend bias resulting from changing of prescription patterns over the pregnancy-related periods.

Figure 3: Illustration of the case-time-control design

Cases were women with pregnancies resulting in miscarriage. A risk-set sampling was used to identify exposure time-trend controls from pregnant women. Control individuals were matched 1:1 to women with miscarriages.

Index date for women with miscarriages was the date of miscarriage diagnosis. For controls, index date was determined by adding the number of days of pregnancy taken from the matched case to the last menstrual period of controls.

The risk period was defined as 1 to 28 days before the index date, and 2 reference periods were defined as 31 to 58 and 181 to 208 days before the last menstrual period, respectively.

Outcome

Miscarriage was defined as any pregnancy loss occurring between the first prenatal care visit (usually 8 weeks) and the 19th completed week of pregnancy.

Exposure

Benzodiazepines included in this study (those in black text are in scope of this review):

- Long-acting benzodiazepines (half-life >24 h): clonazepam, diazepam, chlordiazepoxide, medazepam, bromazepam, clobazam, prazepam, nordazepam, cloxazolam, oxazolam, nitrazepam, flunitrazepam, brotizolam.
- Short-acting benzodiazepines (half-life ≤24 h): oxazepam, clorazepate, lorazepam, alprazolam, fludiazepam, flurazepam, estazolam, triazolam, lormetazepam, temazepam, midazolam, nimetazepam.

Exposure was defined as women receiving at least 1 prescription of benzodiazepine during the risk or reference period. Authors further assessed exposure to short-acting or long-acting benzodiazepines and exposure to the most commonly used individual medicines (alprazolam, diazepam, lorazepam, oxazolam, fludiazepam).

A dose-dependent effect was estimated by mean daily exposure within the risk or reference periods. The mean daily exposure was calculated using the defined daily dose as defined by the WHO collaborating center for drug statistics methodology.

Statistical analyses

Conditional logistic model to estimate odds ratios (ORs) and 95% CIs of miscarriage:

- Case-crossover ORs and exposure time-trend control crossover ORs calculated separately.

- Case-time-control ORs calculated by dividing the case-crossover ORs by the control crossover ORs.

Regression models fitted for case-time-control included an additional interaction term between exposure status in each period and an indicator that identifies an individual as either a case or a control. The regression coefficient for the interaction term provided an adjusted estimated of the OR between benzodiazepine use and miscarriage.

Several sensitivity analyses:

- Redefined exposure assessment period as 7, 14, 56 days to assess impact of exposure duration.
- Extended prescription period by 14 days to evaluate impact of exposure misclassification
- Redefined exposure as having filled at least 2 prescriptions to further minimise exposure misclassification.
- Redefined miscarriage as at least 2 diagnosis codes on different dates to minimise outcome misclassification.
- Used commonly used diagnosis codes or reimbursement codes for miscarriage to further minimise outcome misclassification.
- Adjusted comedication use (eg, antidepressants, opioids, anticonvulsants, z-hypnotics, anxiolytics) to account for time-varying confounders.
- Conducted a negative control analysis by comparing 2 negative risk periods (31-58 and 91-118 days before the last menstrual period) with the reference period (181-208 days before the last menstrual period).

Results

A total of 3,067,122 pregnancies among 1,957,601 women, of which 136,134 (4.4%) resulted in miscarriage. The mean (SD) age of the study population was 30.61 (5.91) years.

After matching with time-trend control individuals, 134,864 pairs of pregnant women had been identified.

Of the pregnancies resulting in miscarriage, 1502 were exposed to benzodiazepines during the risk period only (1-28 days before miscarriage) and 2896 were exposed during the earlier reference period only (181-208 days before the last menstrual period). For time-trend control individuals, 753 and 2386 were exposed during the risk and reference periods, respectively.

The **case-time-control ORs** (Table 4) revealed exposure to benzodiazepines was associated with an increased risk of miscarriage (OR 1.69, 95% CI 1.52-1.87). Analysis of long-acting and short-acting benzodiazepines showed an increased risk of miscarriage with case-time-control ORs of 1.67 (95% CI 1.44-1.93) and 1.66 (95% CI 1.47-1.87), respectively. Similar elevated risks were also observed in analyses using 31 to 58 days before the last menstrual period as the reference period.

Table 4: Associations between pregnancy benzodiazepine use and risk of miscarriage: Case-time-control (CTC) design

In **subgroup analyses**, an increased risk of miscarriage associated with each commonly used individual benzodiazepine was identified, ranging from case-time-control ORs of 1.39 (95% CI 1.17-1.66) for alprazolam to 2.52 (95% CI 1.89-3.36) for fludiazepam (Figure 4). A dose-response association was observed with risk increasing from 1.61 (95% CI 1.43-1.82) for low-dose exposure to 1.86 (95% CI 1.53-2.25) for high-dose exposure.

Figure 4: Associations between pregnancy benzodiazepine use and risk of miscarriage: Subgroup analyses

Sensitivity analyses using risk and reference periods of 7 and 14 days, respectively, and redefining exposure as having filled at least 2 prescriptions yielded estimates generally consistent with the main analysis (Table 5). Redefining exposure assessment period to 56 days and extending the prescription period by 14 days attenuated the risks of miscarriage but were still significantly increased. Consistent results were found in sensitivity analyses that redefined miscarriage using at least 2 diagnoses, adopted commonly used diagnosis codes, and accounted for potential time-varying confounders. In negative control analyses, no increased risk was observed.

Table 5: Associations between benzodiazepine use during pregnancy and risk of miscarriage: Sensitivity analyses

Comments:

The methodology used in this study was unclear and difficult to understand:

- The authors used a case-time-control design. It is thought that by using cases as their own controls, this design reduces the effect of unmeasured confounding factors if exposure varies over time. However, it is unclear how a person can be their own control if they are not pregnant.
- In the case-crossover analysis, cases were women with pregnancies resulting in miscarriage. A risk-set sampling was used to identify exposure time-trend controls from the pregnant women. It is unclear what this means.

Miscarriage was defined as any pregnancy loss occurring between the first prenatal case visit (usually 8 weeks) and the 19th completed week of pregnancy. The exclusion of miscarriages <8 weeks could have resulted in the loss of some cases.

3.1.2 Grigoriadis et al 2020 – Pregnancy and delivery outcomes following benzodiazepine exposure: A systematic review and meta-analysis [25]

Objective

Understanding the effects of benzodiazepines on maternal/fetal health remains incomplete despite their frequent use. This article quantifies the effects of antenatal benzodiazepine exposure on delivery outcomes.

Methods

Medline, PsychINFO, CINAHL, Embase and the Cochrane Library were searched up to 30 June 2018. English-language cohort studies comparing antenatal benzodiazepine exposure to an unexposed group on any delivery outcome were eligible. A total of 23,909 records were screened, 56 studies assessed, and 14 studies included.

Two reviewers independently assessed quality and extracted data. Estimates were pooled using random effects meta-analysis. Sub-analyses examined several potential moderators including timing of exposure.

Results – General

A total of 56 articles were examined for inclusion and 14 were included in the meta-analysis. There were 9 outcomes with sufficient data for meta-analysis. Antenatal benzodiazepine exposure was significantly associated with increased risk of 6 outcomes initially: spontaneous abortion, preterm birth, low birth weight, low Apgar score, neonatal intensive care unit (NICU) admission, and induced abortion.

There was significant heterogeneity between studies for most outcomes without consistent moderators. Birth weight, gestational age, and small for gestational age (SGA) did not show significant associations although after adjusting for publication bias, gestational age and SGA became significant, totalling 8 significant outcomes.

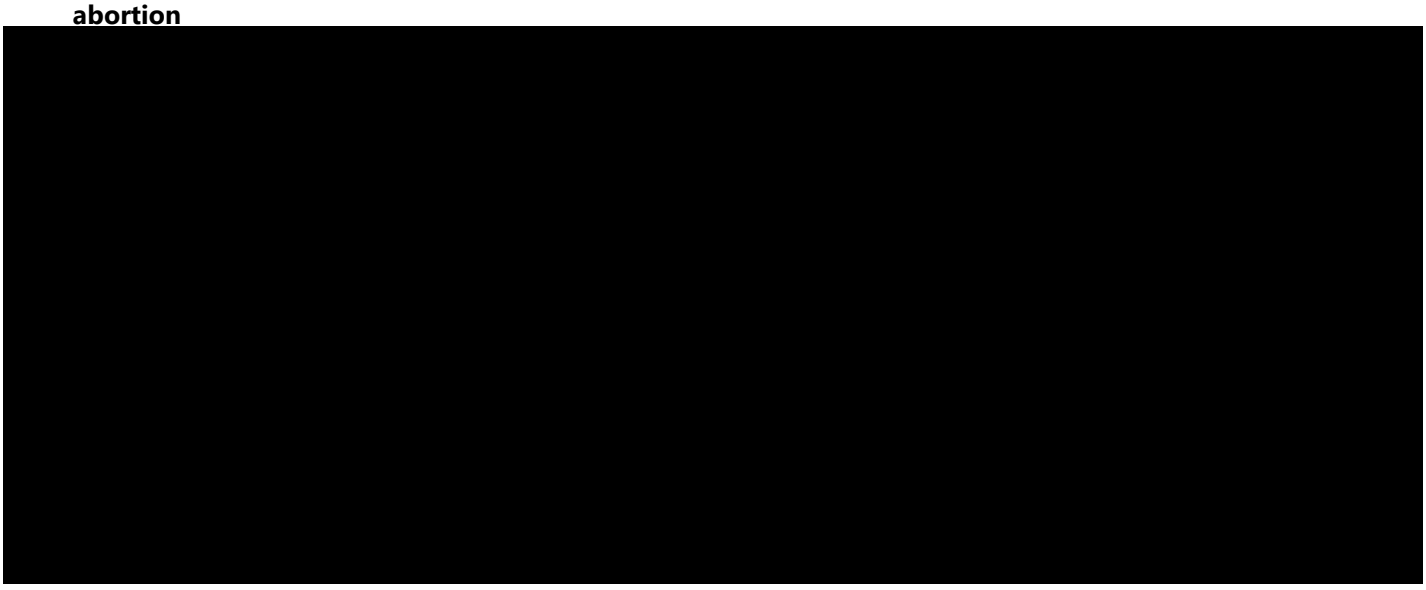
Results – Spontaneous abortion

Spontaneous abortion was significantly associated with benzodiazepine exposure (3,386 exposed and 1,204,620 unexposed) during pregnancy based on 5 pooled studies (OR 1.86, 95% CI 1.43-2.42) although significant heterogeneity across studies was observed, accounting for 76% of the variance (Figure 5).

Figure 5: Pooled odds ratio for spontaneous abortion following antenatal exposure to benzodiazepines

Subgroup analyses examining possible moderators found significant effects for all subgroups although 3 moderators were significant (Table 6). These were timing of exposure (with 'anytime exposure' having the highest OR based on 3 studies), exposure to other psychotropics ('not specified' having a higher OR based on 4 studies), and controlling for psychiatric diagnoses ('not specified' having the highest OR based on 3 studies).

Table 6: Potential moderators of the effect of antenatal benzodiazepine exposure on spontaneous abortion



Publication bias was assessed visually with funnel plot and quantitatively with Egger's test when there were >5 studies. For spontaneous abortion, visual inspection of the funnel plots indicated some publication bias. The revised OR using the trim-and-fill method was slightly attenuated but remained significant (OR 1.43, 95% CI 1.10-1.86).

Comments:

The OR for spontaneous abortion from this meta-analysis was 1.86 which was statistically significant. However, the clinical significance is unclear.

Of the 14 studies included in the meta-analysis, the indication for benzodiazepine use was not known in 4 studies, 2 studies were in women with epilepsy, and 1 study was for obstetrical reasons. The studies that did not report an indication had larger sample sizes. The study populations were likely heterogeneous and confounding by indication could explain some of the associations found.

3.1.4 Ban et al 2012 – Live and non-live pregnancy outcomes among women with depression and anxiety: A population-based study [26]

Objective

To examine the impacts of antenatal depression and anxiety and of commonly prescribed treatments on the risks of non-live pregnancy outcomes.

Methods

The authors identified pregnancies and their outcome (live birth, perinatal death, miscarriage or termination) among women aged 15-45 years between 1990 and 2009 from The Health Improvement Network (THIN) database in the UK.

Depression, anxiety and exposure to medicine were defined according to the presence or absence of a relevant recording in each woman's primary electronic health records within the first 90 days following the estimated date of conception (the first trimester of pregnancy).

The authors extracted records of prescriptions of all antidepressants, hypnotics, and anxiolytics that were primarily indicated for the treatment of depression or anxiety according to British national guidelines (British National Formulary, 57th edition, 2009).

To minimise the risk of detecting reverse-causal effects (where a non-live outcome may be the trigger for depression or anxiety and its treatment), the authors excluded prescriptions and diagnoses within the last 7 days of pregnancies which ended within the first trimester.

Mothers were grouped into eight mutually exclusive categories according to their diagnostic and treatment status:

- Group 0: No history of anxiety or depression (non-exposed)
- Group 1: History of diagnosis of anxiety or depression before pregnancy but no diagnostic recordings during the first trimester.
- Group 2: Diagnostic records of anxiety or depression but no prescriptions of interest during the first trimester.
- Group 3: Prescriptions for any tricyclic antidepressants (TCAs) alone (ie, no other psychotropic medicine of interest) during the first trimester.
- Group 4: Prescriptions for any SSRIs (alone) during the first trimester.
- Group 5: Prescriptions for any benzodiazepines (alone) during the first trimester.
- Group 6: Prescriptions for any other single class of medicines from the following groups during the first trimester:
    - Other sedative medicines: buspirone, meprobamate, zaleplon, zolpidem tartrate, zopiclone, chloral hydrate, triclofos sodium
    - MAOIs: phenelzine, isocarboxazid, tranylcypromine, moclobemide
    - Other antidepressants: duloxetine, mirtazapine, reboxetine, tryptophan, venlafaxine.
- Group 7: Prescriptions for two or more classes of psychotropic medicine (mentioned above) during the first trimester.

Multinomial logistic regression models were used to compare risks of non-live outcomes among these groups, adjusting for major sociodemographic and lifestyle characteristics.

Results

A total of 512,574 pregnancies in 331,414 women were identified.

The prevalence of miscarriage and perinatal death was highest among women prescribed psychotropic medicines, especially those receiving benzodiazepines, the less common medicines (Group 6) and those receiving multiple classes of medicines. In women prescribed benzodiazepines only, 0.7% of pregnancies ended in perinatal death and 16.2% in miscarriage. The equivalent proportions for women with unmedicated

depression or anxiety were 0.6% and 12.1% and for those in the reference group were 0.4% and 12.1%, respectively (Table 7).

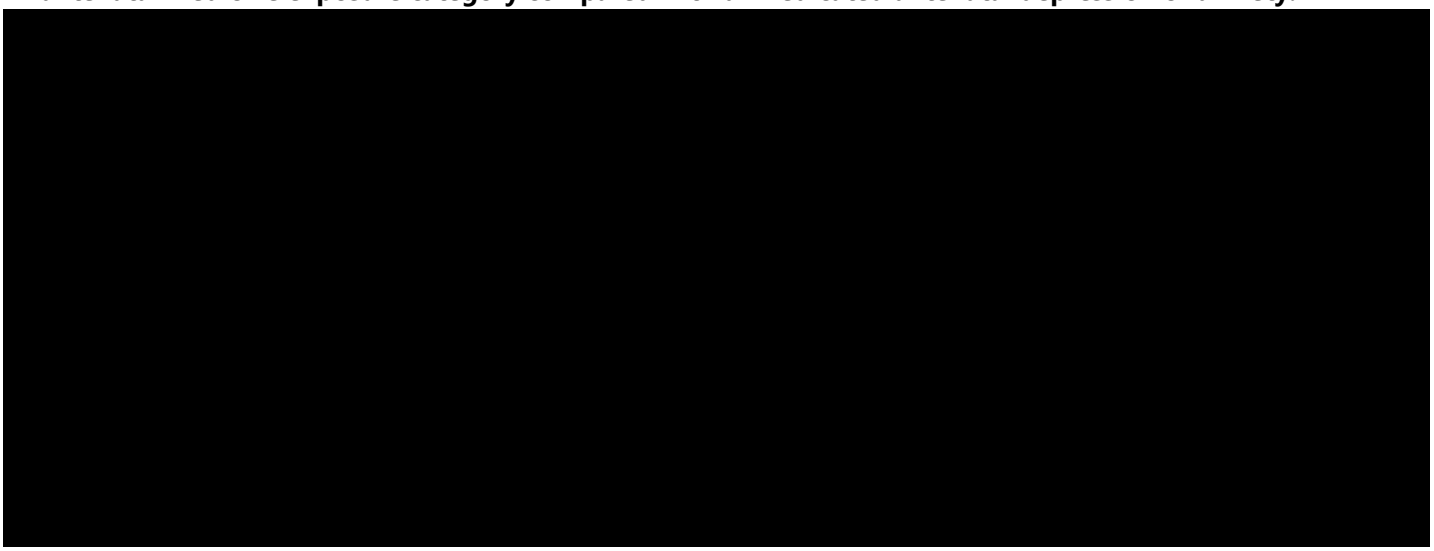
Table 7: Breakdown of live and non-live pregnancy outcomes by different antenatal diagnostic and medicine exposures

Table 8 presents the adjusted relative risk ratios for each adverse outcome for each exposure category compared with the reference group. Compared to women with no current/past, depression or anxiety, women with a history of depression or anxiety and exposure to psychotropic medicines during the first trimester of pregnancy had consistently increased risks of all non-live pregnancy outcomes. Women exposed to benzodiazepines had an increased risk of miscarriage compared with women who had no current/past depression or anxiety (RRR_{adj} 1.6, 99% CI 1.4-1.9).

Table 8: Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and medicine exposure category compared with no current/past depression or anxiety

Compared with pregnancies in women with unmedicated depression or anxiety, women prescribed psychotropic medicines had increased risks of all non-live pregnancy outcomes, although most of the results for perinatal death were not statistically significant at the 1% level (Table 9). Women exposed to benzodiazepines had an increased risk of miscarriage (RRR_{adj} 1.6, 99% CI 1.3-1.9) compared to women with unmedicated depression or anxiety.

Table 9: Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal medicine exposure category compared with unmedicated antenatal depression or anxiety.



Comments:

The benzodiazepines included in this study were selected according to British national guidelines as published in the British National Formulary (BNF, 57th edition, 2009). Medsafe doesn't have access to the BNF so it is unknown which benzodiazepines were specifically included.

Differentiating between past illness, current illness without medicine use, and current medicine use stratified by medicine class were strengths of this study. However, the severity of disease wasn't assessed (eg, women prescribed a medicine could have more severe illness, pregnant women with severe mental illness may be more likely to choose a subsequent termination).

3.1.5 Sheehy et al 2019 – Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion [27]

This was a nested case-control study examining the association of maternal benzodiazepine use by pregnant women and by medicine class, duration of action, and specific benzodiazepines with the risk of spontaneous abortion in Canadian women during early pregnancy.

Methods

Nested case-control study within the Quebec Pregnancy Cohort (Montreal, Quebec, Canada). Includes all pregnancies covered by the Quebec Prescription Drug Insurance Plan from 1 January 1998 to 31 December 2015. Each case was randomly matched with up to 5 controls.

Benzodiazepine exposure was defined as 1 or more filled prescriptions between the first day of the last menstrual period and the index date (the calendar date of spontaneous abortion diagnosis). Benzodiazepine exposure was categorised by overall use, long- or short-acting benzodiazepine, and specific benzodiazepine agents. The specific benzodiazepine agents included in this study were:

- short-acting (half-life ≤24 hours): alprazolam, bromazepam, lorazepam, oxazepam, temazepam, triazolam
- long-acting (half-life >24 hours): chlordiazepoxide, clonazepam, diazepam, flurazepam hydrochloride, nitrazepam).

Spontaneous abortion was defined as a pregnancy loss between the beginning of the 6th week of gestation and the 19th completed week of gestation. Conditional logistic regression models were used to calculate odds ratios (OR) and 95% CIs.

Results

Of the 442,066 pregnancies included in the Quebec Pregnancy Cohort; 27,149 (6.1%) ended with spontaneous abortion with a mean (SD) maternal age of 24.2 (6.5) years. Among pregnancies ending with spontaneous abortion, 375 (1.4%) were among women exposed to benzodiazepines in early pregnancy compared with 788 (0.6%) of the 134,305 matched control pregnancies (crude OR 2.39, 95% CI 2.1-2.73).

Adjusting for potential confounders including maternal mood and anxiety disorders before pregnancy, and compared with non-use, benzodiazepine exposure in early pregnancy was associated with an increased risk of spontaneous abortion (adjusted OR 1.85, 95% CI 1.61-2.12). The risk was similar among pregnancies exposed to short-acting (284 exposed cases; adjusted OR 1.81, 95% CI 1.55-2.12) and long-acting (98 exposed cases; adjusted OR 1.73, 95% CI 1.31-2.28) benzodiazepines during early pregnancy. As shown in Table 10, all benzodiazepine agents were independently associated with an increased risk of spontaneous abortion (range of adjusted ORs from 1.13 for flurazepam to 3.43 for diazepam).

Table 10: Specific benzodiazepine incident exposures during early pregnancy and risk of spontaneous abortion

Comments:

There were 375 (1.4%) spontaneous abortions in women exposed to benzodiazepines compared to 788 (0.6%) of matched controls.

The authors conducted an analysis by individual benzodiazepine agents, but some of the sample sizes were small. For example, the highest adjusted OR of 3.43 was for diazepam and the lowest adjusted OR of 1.13 was for flurazepam, with low numbers of women exposed (12 and 5, respectively). Lorazepam had the largest number of women exposed (n=180) with an adjusted OR of 1.75 (95% CI 1.44-2.14).

Compared to the Ban et al UK study which used prescriptions of benzodiazepines as the measure of exposure, this Canadian study used prescription fills reducing the likelihood of exposure misclassification.

3.2 Spontaneous adverse reaction data

3.2.1 New Zealand

There are 75 reports of miscarriage (PT Spontaneous abortion) in the NZ pharmacovigilance database. The suspect medicines reported in these 75 cases [redacted] The vast majority (n=70) report tozinameran (Comirnaty Pfizer-BioNTech) as the suspect medicine.

There are no reports of miscarriage with any benzodiazepine.

[redacted]

Source: NZ pharmacovigilance database (data extracted via Qlik suspected adverse reactions to medicine app 14 August 2024)

3.2.2 International

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

The non-epilepsy indications of benzodiazepines include severe anxiety, severe insomnia and as a pre-medicant. Symptoms of anxiety and insomnia are not uncommon during pregnancy with an estimated prevalence of 18% and 38%, respectively. There is the potential for benzodiazepines to be used during the early stages of pregnancy, but data sheets and treatment guidelines generally recommend avoiding benzodiazepines during pregnancy.

Miscarriage is a pregnancy that ends on its own before 20 weeks gestation. It is fairly common and affects 1 or 2 in every 10 pregnancies, with most miscarriages (>95%) occurring in the first 12 to 14 weeks of pregnancy.

The recent case-time-control study using data from Taiwanese databases found the use of benzodiazepines during pregnancy was associated with an increased risk of miscarriage (OR 1.69, 95% CI 1.52-1.87). This remained consistent across sensitivity analyses. However, the methodology used in this study was difficult to follow.

A systematic review and meta-analysis in 2020 also found miscarriage was associated with benzodiazepine exposure (OR 1.86, 95% CI 1.43-2.42). A UK study in 2012 found women exposed to benzodiazepines had an increased risk of miscarriage compared to women with unmedicated depression or anxiety (adjusted RRR 1.6, 95% CI 1.3-1.9), and a Canadian study in 2019 found benzodiazepine exposure in early pregnancy was associated with an increased risk of miscarriage compared with non-use (adjusted OR 1.85, 95% CI 1.61-2.12).

Risk estimates from the published literature are fairly consistent and unlikely to significantly change in the near future due to ethical considerations in this patient population.

There have been no spontaneous reports of miscarriage with benzodiazepines in NZ and international data suggests there is no signal of disproportionate reporting.

5 ADVICE SOUGHT

The Committee is asked to advise:

- on the strength of the evidence for an association between the benzodiazepines included in this review and the risk of miscarriage.

6 ANNEXES

1. Meng et al 2023 article

7 REFERENCES

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