



Benzodiazepine utilization during pregnancy and the incidence of pregnancy loss



Benzodiazepines are commonly used for anxiety and sleep disorders. Recently, a safety signal of increased miscarriage risk with benzodiazepines exposure was reported. This DARWIN EU® study aimed to characterize benzodiazepine use during pregnancy and to estimate the incidence of pregnancy loss among users and non-users.

Study overview

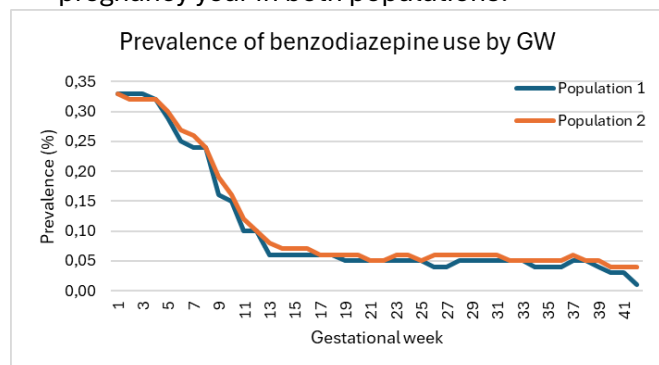
- **Design:** Drug utilization study and descriptive cohort study in Norway and Spain.
- Two **populations** from Norway were included:
 - 1) All pregnancy episodes in 2018-2023 with ≥ 1 year of prior observable data (N=360,912).
 - 2) All pregnancy episodes in 2010-2018 with ≥ 1 year of prior observable data (N=631,098).

Pregnancy episodes were identified using the **UiO Pregnancy Algorithm***, mapped to a **Pregnancy Extension Tables (PET)****.

- **Exposure:** Benzodiazepines (ATC code N05BA and N05CD) at the substance level. Alternative treatments included melatonin, SNRIs, SSRIs, and z-hypnotics.
- User **characteristics** assessed included indication, age at pregnancy start date (last menstrual period [LMP]), selected comorbidities and comedication, pregnancy year, and gestational week (GW).
- **Outcomes:** Incidence of pregnancy loss with outcome-specific windows:
Miscarriage: From LMP to GW20.
Stillbirth: From GW20 to end of pregnancy date.

Benzodiazepine use in pregnancy in Norway

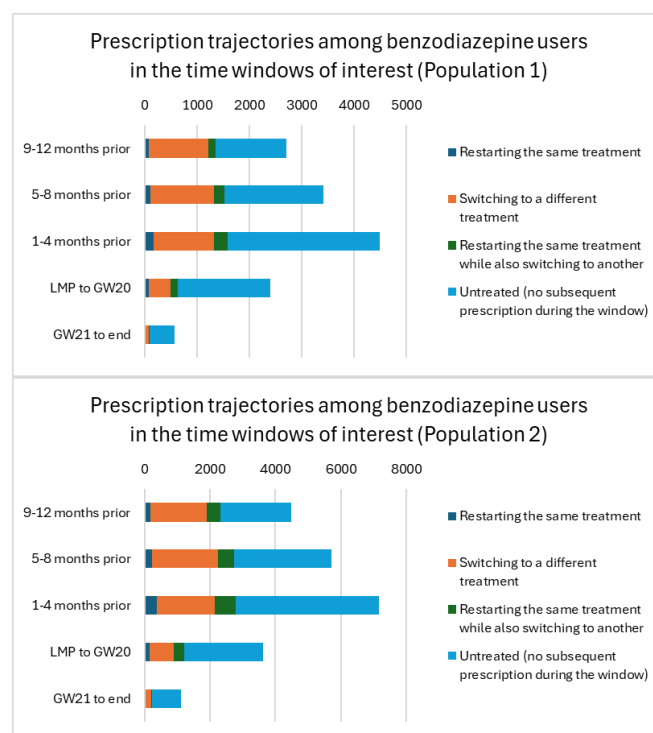
- Benzodiazepine exposure occurred in **0.9% of pregnancies** and remained stable by pregnancy year in both populations.



- SSRIs (prevalence 2.1-2.7%) were the most frequently used alternative drugs, followed by z-hypnotics (1.0-1.1%), melatonin (0.4-0.9%), and SNRIs (0.3-0.4%).

Characterization of benzodiazepine treatment during pregnancy in Norway

- **Most frequently used** benzodiazepines were oxazepam (0.5-0.6%), diazepam (0.3-0.4%), and nitrazepam (0.04-0.1%).
- Use was generally **short-term** (<4 weeks), in line with clinical guidelines.
- The **median duration** of the first dispensation of benzodiazepines was 8 days (IQR 6-19) in population 1 and 11 days (IQR 6-22) in population 2.



- The observed trajectories align with **clinical guidance and patient behavior**: many women discontinue benzodiazepines when planning pregnancy or early in gestation.
- Switching between treatments was more frequent **pre-pregnancy** (36-42%) and decreased steadily during pregnancy, lowest in late pregnancy (14-17%).
- Absolute exposure counts increased during the year prior to, peaked **0-4 months before pregnancy**, and declined to the lowest levels in late pregnancy.

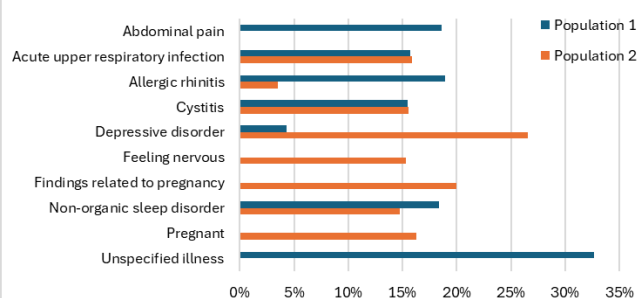
* Nordeng H, et al. *Pharmacoepidemiol Drug Saf* 2024;33:e70002.

** PETs are specialized tables that standardize how pregnancy and newborn data are represented in the OMOP common data model.

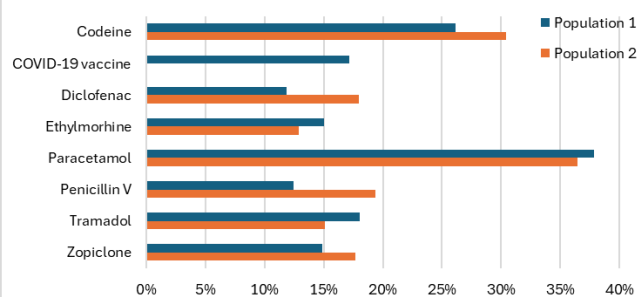
Characteristics of benzodiazepine users during pregnancy in Norway

- There was **no recorded indication** in the year before LMP for 42.5% of benzodiazepine users in pregnancy in population 1, compared to 45.1% in population 2.
- Anxiety was the most common **indication** (17–26%), followed by combined anxiety and mental health disorders (8.2–11.2%) and mental health disorders alone (6.4–14.2%).
- The **median age** of pregnant benzodiazepine users was 32 (IQR 28–36) years in population 1 and 30 (26–34) years in population 2.

Most common comorbidities in the year before LMP among benzodiazepine users in pregnancy



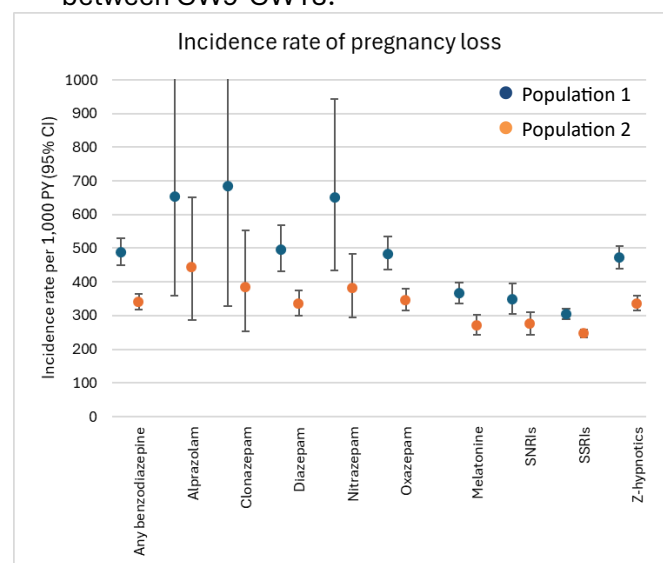
Most common comedications in the year before LMP among benzodiazepine users in pregnancy



- **Healthcare utilization** in the year before LMP was high with a median of 27 (IQR 15–48) visits in population 1 and 15 (7–29) in population 2.

Incidence of pregnancy loss in Norway

- The **incidence of pregnancy loss** was 248 per 1,000 person-years (PY) (95% CI 246–250) in population 1 and 206 per 1,000 PY (205–208) in population 2. Miscarriage accounted for the majority of events, with the highest values between GW9–GW13.



Data & Methods notes

- A substantial proportion of pregnancies **lacked an indication** in the year before LMP. This limits the ability to control for confounding by indication in a safety study. Expanding the look-back period or broadening the list with codes for potential indication may improve this.
- Assumptions regarding treatment duration (e.g. 1 DDD per day and a 30-day permissible gap for drug eras) may overestimate exposure duration.
- Some pregnancy outcomes, particularly **early losses and terminations**, may be under-recorded depending on coding practices and care setting coverage.

How was this useful?

Benzodiazepine exposure was identified in approximately 1% of pregnancies in Norway, consistent with previously reported prevalence values. Use of benzodiazepine was highest at LMP and declined throughout gestation, likely reflecting intentional discontinuation due to pregnancy or clinical guidance. Among benzodiazepine-exposed pregnancies, **incidence of loss** ranged from 340 to 488 per 1,000 PY. Crude rates were numerically higher than in all pregnancies (206–248 per 1,000 PY), but these unadjusted figures should not be interpreted as indicative of increased risk, as no comparative analyses were conducted.

Access to the full report

[DARWIN EU® – Utilisation of commonly used benzodiazepines during pregnancy and the incidence of pregnancy losses](#)

Contact

Hedvig Nordeng:
h.m.e.nordeng@farmasi.uio.no