Maternal and neonatal outcomes after benzodiazepine and benzodiazepine agonist exposure during pregnancy in women with mental disorders

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Abstract

Abstract Objective To compare the gestational age of neonates in utero exposed to benzodiazepines (BDZs) with none exposed controls. Secondary objectives were; birth weight, presence of congenital malformations, APGAR score, and the need for > 3 months (prolonged) maternal psychiatric care. Study design A retrospective cohort study of women and neonates from 2013 to 2021 with univariate and multivariable analysis to study the associations between BDZs exposure and gestational age compared to non-exposed women with mental health problems. Results We found that BDZ exposure was associated with a lower gestational age of -3.2 days (95% CI -5.8 , -0.53 days). Women in the exposed group had an increased risk of psychiatric care (adjusted OR 2.511 (95% CI 1.675 – 3.782), p < 0.001). Conclusion We found that in utero BDZ exposure was independently associated with a significantly lower gestational age of the neonates and prolonged psychiatric care of their mothers.

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Patient Consent

Consent to publish this cohort study was not obtained, as decided by the medical ethical review board. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship. None of the authors have any conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

What is already known about this subject?

Benzodiazepines are thought to decrease the duration of pregnancy, lower the APGAR scores of the neonate, and decrease birth weight of the neonate.

What this study adds

The use of benzodiazepines during pregnancy did not negatively affect maternal and neonatal outcomes after inclusion of possible confounders in the dataset

Using Directed Acyclic Graphs (DAGs) is of use in the setting of pregnancies complicated by psychiatric diseases and psychotropic drugs and other co-morbidities and demographic parameters

Abstract

Objective

To compare the gestational age of neonates in utero exposed to benzodiazepines (BDZs) with none exposed controls. Secondary objectives were; birth weight, presence of congenital malformations, APGAR score, and the need for $>$ 3 months (prolonged) maternal psychiatric care.

Study design

A retrospective cohort study of women and neonates from 2013 to 2021 with univariate and multivariable analysis to study the associations between BDZs exposure and gestational age compared to non-exposed women with mental health problems.

Results

We found that BDZ exposure was associated with a lower gestational age of -3.2 days (95% CI -5.8 , -0.53 days). Women in the exposed group had an increased risk of psychiatric care (adjusted OR 2.511 (95% CI 1.675 – 3.782), $p < 0.001$).

Conclusion

We found that in utero BDZ exposure was independently associated with a significantly lower gestational age of the neonates and prolonged psychiatric care of their mothers.

Keywords

- Benzodiazepines
- Pregnancy
- Neonatal complications
- Maternal complications
- Retrospective cohort study

Introduction

The risk for mental disorders during life is high, especially for women at fertile age, with a prevalence of 20-44% for any mental disorder during pregnancy and a relapse rate during pregnancy of 43-50%. Prior studies indicate that mental disorders during pregnancy are associated with an increased risk of preterm birth, low birth weight, and low APGAR scores.

Benzodiazepines including the agonist zopiclone and zolpidem, (together BDZs) are commonly used psychotropic drugs for mental disorders during pregnancy. BDZs act on the GABA-A receptor by increasing

the inhibitory effect of y-aminobutyric acid (GABA), which leads to the opening of chloride channels, hyperpolarization of the cell membrane, and inhibition of excitation of the central nervous system. A systematic review and meta-analysis conducted by Bais et al in 2019 in 28 countries showed that the use of BDZs during pregnancy is common, with a prevalence of 3.1% (95% CI 1.8% , 4.5%). BDZs cross the placenta and may accumulate in fetal tissues. A recent systematic review and meta-analysis from Grigoriadis in 2020 included 14 cohort studies and showed that exposure to BDZs in pregnancy was significantly associated with an increased risk of spontaneous abortion (OR 1.86, 95% CI 1.43, 2.42), low birth weight (OR 2.24, 95% CI 1.41, 3.88), low APGAR score (OR 2.19, 95% CI 1.94, 2.47), preterm birth (OR 1.96, 95% CI 1.25, 3.08), induced abortion (OR 2.04 CI 95% 1.23 , 3.40) and admission to the NICU (OR 2.61 95% CI 1.64, 4.14).

The teratogenicity of BDZs is however still under debate. A meta-analysis from *Enato et al* in 2011 showed no increased risk for major malformations and oral cleft in cohort studies (OR 1.07 (95% CI 0.9, 1.25)), while analysis of case-control studies showed an association between major malformations (OR 3.01 95% (CI 1.32, 6.84)) and oral clefts alone (OR 1.79 95% (CI 1.13, 2.82)) after BDZ exposure in the first trimester. In case-control studies, cardiac malformations were not significantly increased. A more recent meta-analysis of Grigoriadis in 2020 with only cohort studies confirms these results and showed no significant association with congenital malformations (OR 1.13 95% (CI 0.99, 1.30)) and cardiac malformations (OR 1.27 (95% CI 0.98, 1.65)) after BDZ exposure. However, a combination of BDZs and antidepressants increased the risk of congenital malformations significantly (OR 1.40 95% (CI 1.09, 1.80)). In the Netherlands, the use of BDZs during pregnancy is carefully considered, as described in the guidelines for benzodiazepines in pregnancy and childbirth of the Dutch Association of Obstetrics and Gynaecology (NVOG).

Studies on BDZs during pregnancy often used large databases without overseeing the indication or diagnosis of use and often lack determination of possible confounding variables. To our knowledge, this is the first study on the effect of BDZs exposure in pregnancy on neonatal and maternal outcomes, including possible confounders. Our primary aim was to investigate the potential association of BDZs exposure during pregnancy with gestational age, and our secondary aims are to determine the potential association with birth weight, presence of congenital malformations, APGAR score, and the need for prolonged psychiatric care.

Materials, subjects and methods

Study design and setting

This explorative retrospective cohort study was conducted in Isala, a large teaching hospital in Zwolle, the Netherlands. Pregnant women treated in our hospital and women who were referred from primary care or regional hospitals to our hospital were included. The period of inclusion was from the introduction of national guidelines on the use of BDZs during pregnancy on 01-01-2013 until 31-12-2020 with a (poli)clinical delivery or puerperium in our hospital.

Participants

We included pregnant women between 18 and 45 years with a diagnosed mental disorder using psychotropic drugs and/or having at least two (poli)clinical consults from a mental care provider in our hospital. We divided the included patients into two groups, a BDZs-exposed and a reference group not using BDZs.

Exposure

The exposed group consisted of pregnant women exposed to BDZs and/or hypnotic benzodiazepine receptor agonists (BDZs), BDZs exposure was defined as using chronic BDZs any time from the first day of the last menstrual period (LMP) until the end of the pregnancy. The LMP was estimated from the gestational age reported in the patient file.

Exclusion criteria for both groups were a stillbirth delivery ($>$ 24 weeks of gestation) and multiple births. Also, pregnancies with exposure to teratogenic drugs according to the Teratology Information Centre (TIS) were excluded. However, we included lithium because of its indication in bipolar disorders. Mother-child couples were excluded in the case of paternal or maternal congenital malformations according to ICD-10 codes

class XVII (Q00-Q99) or in the case of an actual maternal diagnosis of epilepsy (ICD-10 G40-G41), because of the possibility of using teratogenic anti-epileptic drugs. Further, mother-child couples with missing primary or secondary outcomes were also excluded. Women with short-term use of BDZs only used during hospital admission were excluded as these might bias the results because it's not related to psychiatric disease. In the presence of more than one pregnancy concerning the same mother, we randomly selected one pregnancy in our dataset. For statistical reasons, we included a double number of pregnancies in the reference group at random compared to the exposed group.

Outcomes

We compared the exposed and reference group using gestational age (days) as the primary outcome. Secondary outcomes were birth weight, APGAR scores at 1 and 5 minutes, presence of congenital malformations, and prolonged psychiatric care defined as > 3 months postpartum psychiatric care.

Congenital malformations were divided into minor and major malformations according to EUROCAT guidelines if an ICD-10 codes class XVII (Q00-99) was recorded in the EPF. Prolonged psychiatric care of the mother was defined as more than 3 months postpartum, which is the normal follow-up time. The severity of the underlying mental disorder was estimated by the total number of registered mental disorders.

The reference group consisted of pregnancies of women with any mental disorder not using a BDZ at any time during pregnancy.

Covariates

The primary and secondary outcomes may be a priori confounded by other factors, like gender because of higher birth weights in male infants compared to female infants. Maternal age at the time of conception, BMI before pregnancy, educational level (low/middle/high), presence of support system (defined as an in-house living partner) and smoking, drugs, and alcohol use during pregnancy, may be associated with birth weight and complications during delivery. The number and type of actual and historical mental disorders mentioned in the patient file and the use of concomitant other psychotropic drugs during pregnancy may affect primary and secondary outcomes, and so were recorded. Other possible confounders may be chronic comorbid disorders, such as thyroid disease and asthma, and pregnancy-related disorders, like (gestational) diabetes, hypertension, pre-eclampsia/HELLP, and infections during pregnancy. Further, information about the parity (0/1+), a previous miscarriage/abortion, and the use of IVF/ICSI were collected. The use of epidural/spinal anesthesia during delivery, position during delivery, gender of the newborn, and presence of meconium may influence the primary and secondary outcomes, and were also recorded.

Data source and data collection

Women eligible for the study were found using CTcue®, an Artificial Intelligence searching program developed to collect data from Electronic Patient Files (EPF) of our clinic (CTcue®, version 2.1.1.10, Amsterdam, Netherlands). Data were collected in CTcue® and further processed in Rstudio.

Statistical methods

A directed acyclic graph (DAG) was constructed by using the online DAGitty software (http://www.dagitty.net/) to select covariates for inclusion in the statistical models.

The relationships between each of the variables were assigned based on knowledge of the publications regarding these associations. Concerning assumptions described in the DAG theory, a minimal sufficient set of adjustment variables was identified for estimating the effect of BDZs use on maternal and neonatal risks.

Descriptive statistics

Continuous data were presented as mean ($\pm$sd) or median (... - ...), depending on the distribution. Normality of the data was tested with a visual inspection of the data, the Shapiro-Wilk test, and comparing means with medians. Categorical data were presented as n(%).

Inferential statistics

Variables concerning the exposed and reference group were compared using the independent samples T-test, Pearson's Chi-square test, or Fisher's exact test whenever applicable.

Regression analyses on the primary (gestational age) and secondary outcomes (birth weight, APGAR scores, congenital malformations, and prolonged psychiatric care) were performed to adjust the study group (BDZ-exposed versus reference group) for confounding variables.

Comparison of baseline characteristics ($p<0.05$) and univariate regression analyses were performed to select potential confounders. Variables with a p-value <0.1 by univariate analysis were entered in the multivariable regression model for backward regression analysis. Variables with a non-obvious time relationship with the investigated outcome (e.g. epidural/spinal anesthesia and gestational age), were excluded from the multivariable model. All statistical tests were performed using Rstudio.

Ethical approval

The Daily Board of the Medical Ethics Committee Isala Zwolle, The Netherlands, has reviewed this study. As a result, the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO), do not apply to this research proposal.

Our findings are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Results

Participants

We identified 201 pregnancies exposed to the BDZ group and 386 pregnancies not exposed to BDZ in the period of interest. In the exposed group, six pregnancies were excluded because of multiple births and one for a stillbirth. Of the remaining 194 singleton live birth pregnancies in the exposed group, a total of 25 pregnancies were excluded for the following reasons: pregnancies with an actual diagnosis of epilepsy, pregnancies with congenital malformations in one of the parents, or exposure to teratogenic drugs. For the same reasons and due to missing data about the primary and secondary outcomes, 42 pregnancies were excluded and nine multiple births pregnancies from the reference group.

As a result, 169 pregnancies in the exposed group and 335 pregnancies in the reference group were eligible. In presence of more than one pregnancy from the same mother we randomly selected a pregnancy in our dataset. See figure 1 for the details on patient selection. The final dataset consisted of 147 pregnancies in the exposed group and 294 pregnancies in the reference group.

Both groups differed in maternal and clinical characteristics, see table 1. In the BDZs exposed women used more alcohol during pregnancy (4.1% vs 0.7%, $p = 0.019$), had lower number of mental disorders ($p=0.010$), a higher number of concomitant psychotropics ($p<0.001$), and needed longer psychiatric care after delivery ($p<0.001$), see table 1. Duration of pregnancy was shorter in the BDZs exposed group, 269 days for the exposed group and 274 days for the non-exposed group, $p<0.001$.

BDZ-exposure

In 26.5% of the pregnancies, exposure to BDZ was in at least the first trimester, while the exposure was in at least the third trimester (91.8%). In 20.4%, exposure occurred in all trimesters.

We found no differences in both groups regarding birth weight, APGAR scores at 1, 5 and 10 minutes and the number of minor and major malformations. BDZs exposure was associated with a decreased number of gestational days (duration of pregnancy) of -3.2 days, 95% CI -5.8 - -0.53, $p = 0.019$. In the final regression model, also gestational diabetes, preeclampsia or HELLP syndrome, maternal infections, placental disease, meconium containing amnion fluid, lower birth weight and appearance of minor malformations were relevant

factors for decreased number of gestational days. See table 2 for details. The factors APGAR score at 1 and 5 minutes seems not logically related to number of gestational days.

BDZs exposure was associated with prolonged psychiatric care, which was defined as more than 3 months psychiatric care after delivery, OR 2.511, 95% CI 1.675-3.782, p<0.001. Other factors in the model were maternal age, male gender of the newborn and birthweight, see table 3 for details.

We found no differences between minor malformations between the exposed and control group with a crude OR = 1.852 (95% CI 0.897, 3.822), and also no differences in major malformations with a crude OR = 0.652 (95% CI 0.253, 1.680).

Discussion

In this study, we found that in utero exposure to BDZs in women with a mental disorder(s) was associated with a significantly lower gestational age 3.2 days, 95% CI -5.8 - -0.53, p = 0.019. We also found that the use of BDZs during pregnancy is associated with prolonged psychiatric care after delivery concerning the mother. Other parameters like birth weightthe presence of congenital malformations, and the APGAR scores, were not different compared to non-exposure of BDZs.

Concerning the lower gestational age, our results are in line with Huitfeldt et al. and Grigoriadis et al. Huitfeldt et al reported in 2020 a reduction of gestational age of 2.1 days ((95% CI -3.3 - -0.9 days) after in utero exposure of BDZs. The recent systematic review and meta-analysis by Grigoridaris et al in 2020 included studies with prospectively collected data concerning a BDZ exposed and non-exposed cohort, regardless of psychiatric disease, and excluded co-exposure with other psychotropic drugs. They found that exposure to BDZs was associated with a reduction of 6.2 in gestational age (MD – 6.2 days weeks (95% CI -11.2 days - 0.01), P = 0.02). These results, together with our results, a significant shorter gestational age, seems not to be of clinical relevance. Other studies lack information about the indication of use, which might have biased the results. Our cohort comprises BDZs exposure with exposure to other psychotropic drugs, also possible/usable in general clinical care. We found that co-administered psychotropic drugs did not contribute to the lower gestational age. An explanation from a clinical perspective could be that women using BDZs at the end of pregnancy, are more prone to inducing birth and so a shorter duration of pregnancy, possibly because of fatigue symptoms in this vulnerable population and the associated risks of post-partum depression.

We found no association of BDZs exposure with birthweight which indicates that BDZs exposure in utero does not alter the intrauterine growth of the fetus. Our results are conflicting with the results of *Grigoriadis et al.* in 2020 who found that SGA differed significantly between BDZ exposed and non-exposed cohorts after correction for publication bias (OR 1.38 (95% CI 1.04, 1.85), P = 0.03), however, the indication for use was not given. Wang et al in 2010 found also an increase in the proportion of SGA among women using BDZs.

We found no significant association between BDZs exposure and the risk for minor and major congenital malformations in our study, where 26.5% of the women in our cohort were exposed to BDZs during the first trimester. Our results are in line with a meta-analysis of Eneto et al (2011). They included studies with BDZ exposure in at least the first trimester with an unexposed control group with only live births and found no association with major malformations (OR 1.06 (95% CI 0.91, 1.25)) or oral clefts (OR 1.19 (95% CI 0.34, 4.15)) in cohort studies. However, in case-control studies, they found an association between major malformations (OR 3.01 (95% CI 1.32, 6.84)) or oral clefts (OR 1.79 (95% CI 1.13, 2.82)) and BDZ exposure. The included case-control studies may be hampered by recall bias from exposed neonates and the use of concomitant co-medication. A recent meta-analysis by Grigoriadis et al (2019) included cohort studies with prospectively collected data about major congenital malformations and cardiac malformations in BDZ exposed and unexposed pregnancies with live births. They found no association with congenital (OR 1.08 (985% CI 0.93, 1.25)) and cardiac malformations (OR 1.27 (95% CI 0.98, 1.65)) and BDZ exposure alone. However, the risk of malformations increased in a sub-group of women using BDZ and antidepressants with an OR of 1.40 (95% CI 1.09, 1.80)). It is not clear whether these results were due to combined exposure to BDZ and antidepressants or antidepressants exposure alone, which is associated with cardiac malformations.

We found no differences in major malformations in the exposed group (4.1%) compared to the reference group (6.1%) after exclusion of some risk factors for the development of congenital malformations, such as teratogenic drugs. EUROCAT reported a prevalence of 2.33% of major congenital malformations in live births in the Netherlands between 2011 and 2018, which seems lower compared to our study population. An explanation could be that our cohort consists of women with a high-risk pregnancy and delivery or puerperium in the hospital, which could increase the selection and surveillance for congenital malformations. All women in our study had a mental disorder, which is also a risk factor and related to other risk factors for congenital malformations, such as smoking or drug use.

Previous studies reported that the percentage of minor malformations ranged from 14.7% to 40.7%. We found 7.3% minor malformations in our cohort, however, minor malformations were also not consequently reported, screened, and diagnosed. Minor malformations can be used to detect different syndromes or major congenital malformations, especially related to teratogenics which we did not find. However, these data must be interpreted cautiously because of methodological issues about their variation in definition, diagnosis, and reporting.

Strengths and limitations

Observational studies are, by their nature, limited in their ability to establish causation with certainty. Consequently, our results are not necessarily reflective of a causal relationship.

It could be that the effects we found, were due to the severity of illness, which we didn't measure. That is, women with more severe illness may have stayed on the drug, and thus, the illness, and not necessarily the drug, may have affected the effects. This limitation is a result of confounding, that is, the BZD association is distorted because other factors that the study groups differ on, such as diagnosis or indication, can also be associated with adverse outcomes. Effects of confounding by indication can explain a portion or all of the associations found.

However, we tried to reduce selection and confounding bias by using a DAG and using potential confounders published in literature.

Our results are limited by relatively small sample size, and so our findings should be interpreted with caution. Unfortunately, we could not register the use of drugs by trimester of pregnancy. Therefore, any influence of drugs during the organogenesis and the prevalence of congenital malformations in our population could not be directly related to the use of drugs, including BDZs.

In the exposed group the use of BDZs was grouped, regardless of indication, dosage, or half-life of individual drugs. These factors were accounted for by introducing the severity of illness (intermittent versus continuous use of BDZs (data not shown); the number of registered mental illnesses; use of other psychotropic drugs), introducing risk factors for mental disease (educational level; presence of support system), however, we did not find differences between both groups. Although residual confounding could be possible.

Further, it could be that we underestimated the number of congenital malformations, as we only considered live births in our cohort. Therefore, miscarriages and planned abortions may have contributed to the number of malformations.

From the literature, we know that there may be an association between BDZ exposure and miscarriages, but this needs further study. and it could be that children with specific malformations were lost to follow-up because of their specific malformations and further treatment in a tertiary clinic.

Finally, the study population is a high-risk population of pregnant women with severe mental disorders who are referred to our hospital. Women using BDZ while pregnant and treated by their general practitioner were not included. This might overestimate the risks we found and limit our study's generalizability.

One of the strengths of our study is that only women are included with a defined BDZ-exposure for a mental disorder, determined by a manual review of the EPD. We used a rich dataset, including all main possible confounders, to analyze our data, including dosage of BDZ, the indication of use, frequency and duration of

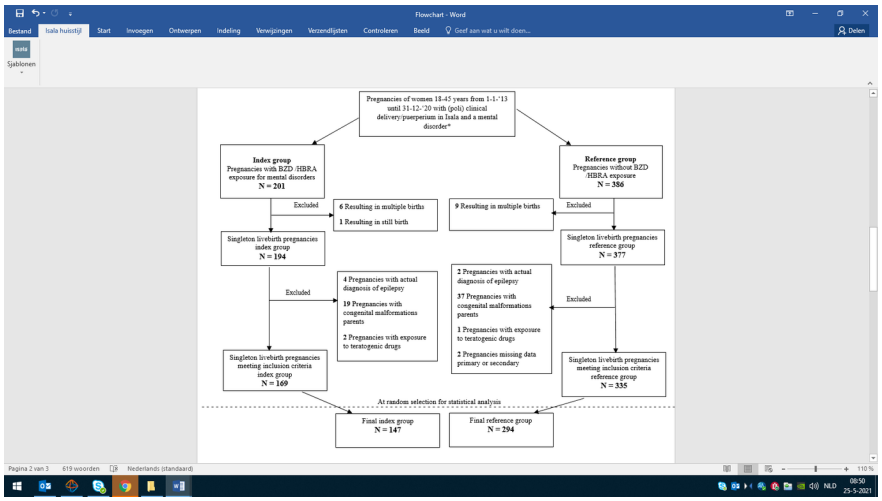
use, and excluding occasional use of BDZ at the end of pregnancy during hospitalization. This may prevent misclassification.

Also, our reference group were women with mental disorders not using BDZs. We know that mental disorders themselves can also lead to different adverse neonatal and maternal outcomes. So confounding by indication might therefore be limited in our study.

Conclusion

We found that neonates in utero exposed to BDZs had a statistically significant lower gestational age of -3.2 days compared to neonates not exposed to BDZs in mothers with mental disorders. This difference seems not clinically relevant. We also found that the use of BDZs during pregnancy is associated with prolonged psychiatric care after delivery concerning the mother. We found no differences between exposed or none exposed to BDZs regarding birth weight, the number of congenital malformations, APGAR score, and the need for prolonged psychiatric care.

References



*See for more details of the inclusion criteria and exclusion criteria in the method section

Table 1: Patient characteristics of the exposed and control group

	Characteristic	No benzodiazepine exposure, N
Maternal	Benzodiazepine exposure only in first trimester, n (%)	0 (NA)
	Benzodiazepine exposure only in second trimester, n (%)	0 (NA)
	Benzodiazepine exposure only in third trimester, n (%)	0 (NA)
	Maternalage, Median (IQR)	31.0 (26.2 – 34.0)
	Body Mass Index (BMI), Median (IQR)	24.8 (21.8 – 28.4)
	Primiparous, n (%)	156 (53)
	Use of Assisted Reproductive Technique, n (%)	17 (5.8)
	Smoking during pregnancy, n (%)	60 (20)
	Alcohol use during pregnancy, n (%)	2 (0.7)
	Drugs use during pregnancy, n (%)	18 (6.1)
	Educational level, n (%)	
	High	98 (33)
	Low	54 (18)
	Middle	122 (41)

	Presence of support, n (%)	275 (94)
	Number of concomitant mental disorders, n (%)	
	1	101 (34)
	2	99 (34)
	3	67 (23)
	4	19 (6.5)
	5	6 (2.0)
	6	2 (0.7)
	Number of other psychotropic drugs, n (%)	
	0	120 (41)
	1	145 (49)
	2	26 (8.8)
	3	3 (1.0)
	4	0 (0)
	Need for prolonged psychiatric care (>3 months post partum, n (%)	93 (32)
	Having gestational diabetes, n (%)	27 (9.2)
	Having thyroid disease, n (%)	13 (4.4)
	Having hypertension, n (%)	30 (10)
	Preeclampsia or HELLP during pregnancy, n (%)	8 (2.7)
	Maternal infections, n (%)	53 (18)
	Having astma, n (%)	41 (14)
	Having Placentaldisease, n (%)	37 (13)
	Use of epiduraal anesthesia during delivery, n (%)	160 (54)
	Unknown	294
	Breech position of the child , n (%)	11 (3.7)
	Meconium containing amnion fluid, n (%)	44 (15)
Neonatal	gender, n (%)	
	f	151 (51)
	m	143 (49)
	Number of gestational days, Median (IQR)	274 (267 – 282)
	Birth weight, Median (IQR)	3,390 (3,090 – 3,689)
	APGAR score at 1 minute, Median (IQR)	9.00 (8.00 – 9.00)
	APGAR score at 5 minutes, n (%)	
	3	1 (0.3)
	5	1 (0.3)
	6	3 (1.0)
	7	8 (2.7)
	8	12 (4.1)
	9	59 (20)
	10	207 (71)
	Unknown	3
	APGAR score at 10 minutes, n (%)	
	3	1 (0.8)
	5	1 (0.8)
	6	1 (0.8)
	7	2 (1.5)
	8	5 (3.8)
	9	16 (12)
	10	106 (80)
	Unknown	162
	Minor malformations, n (%)	17 (5.8)

Major malforomations, n (%)		18 (6.1)
[1]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test		[1]Wilcoxon rank sum test; Fisher's ex

Table 2: Factors associated with number of gestational days

Characteristic	**N**	**Beta**	**95% CI[1]**
Benzodiazepine exposure during pregnancy	441	-3.2	-5.8 to -0.53
Benzodiazepine exposure only in first trimester	147	-4.4	-8.8 to 0.00
Having gestational diabetes	441	-7.4	-12 to -2.9
Having preeclampsia or HELLP	441	-12	-19 to -5.8
Maternal infections	441	-6.1	-9.2 to -3.0
Having placental disease	441	-6.3	-10 to -2.5
Meconium containing amnion fluid	441	7.3	3.7 to 11
Birth weight	441	0.02	0.01 to 0.02
APGAR score at 1 minute	*433*	*1.2*	*0.23 to 2.1*
APGAR score at 5 minutes	*433*	*2.2*	*0.89 to 3.5*
Minor malformations	441	-5.2	-10 to -0.41
[1]CI = Confidence Interval	[1]CI = Confidence Interval	[1]CI = Confidence Interval	[1]CI = Confidenc

Table 3: factors associated with prolonged psychiatric care (> 3 months post partum)

Characteristic	**N**	**OR[1]**
Benzodiazepine exposure during pregnancy	441	2.511
Maternal age	441	1.047
Gender of the neonate	441	
Male		1.499
Birth weight	441	1.000
[1]OR = Odds Ratio, CI = Confidence Interval	[1]OR = Odds Ratio, CI = Confidence Interval	[1]OR = Odds Ratio, CI =

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`figure 1.docx` available at https://authorea.com/users/568235/articles/614187-maternal-and-neonatal-outcomes-after-benzodiazepine-and-benzodiazepine-agonist-exposure-during-pregnancy-in-women-with-mental-disorders