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Research Article

Benzodiazepine Exposure in Pregnancy: A Prospective Study of Outcomes

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Abstract

Purpose: The purpose of this study was to evaluate maternal and neonatal outcomes in women with benzodiazepine exposure during pregnancy.

Methods: Women with neuropsychiatric illness were enrolled prior to 16 weeks' gestation in a prospective study. Inclusion criteria included: 1) Structured Clinical Interview for DSM-IV, 2) complete obstetrical and neonatal records, and 3) singleton pregnancy. Benzodiazepine exposure was defined as cumulative ≥ two weeks at any point in pregnancy, a priori. Primary outcomes included preterm delivery, low birth weight, and cesarean delivery. Logistic regression models were used in examining the associations between benzodiazepine exposure and outcomes.

Results: 633 women were included in the study. 133 (21.0%) were exposed to benzodiazepines during pregnancy. There was a significant interaction effect between women with benzodiazepine exposure and self-reported tobacco use for low birth weight (OR=6.88, 95% CI 1.44–32.75). For women without diagnosis of Posttraumatic Stress Disorder (PTSD), benzodiazepine use was associated with greater odds of cesarean section delivery (OR= 3.12, 95% CI 1.64-5.94). Women with benzodiazepine use were more likely to have preterm delivery if their pregnancy was not planned (OR=3.69, 95% CI 1.40-9.71). Female infants with benzodiazepine exposure were more likely to require special nursery admission (OR= 2.61, 95% CI 1.11-6.13)

Conclusions: The potential adverse effects of benzodiazepine exposure in this cohort were dependent upon other maternal factors such as tobacco use and/or intentionality of pregnancy underscoring the need to carefully characterize populations before assigning reproductive safety risks.

Keywords: Benzodiazepine; Exposure; Pregnancy; Outcome

Introduction

The use of benzodiazepines continues to increase with current estimates suggesting 37.6 benzodiazepine prescriptions filled per 100 persons in the United States in 2012 [1]. Despite the potential for misuse and abuse, benzodiazepines are used in a variety of conditions such as epilepsy, dystonia, spasticity, anxiety and insomnia. It is common to avoid or discontinue benzodiazepine use during pregnancy. The American College of Obstetricians and Gynecologists practice bulletin regarding use of psychotropic medications during pregnancy and lactation suggest use of benzodiazepines for treatment of anxiety during pregnancy as a reasonable option although these medications should be used with caution [2]. Benzodiazepines appear to readily cross the human placenta and enter breast milk at varying levels based on pharmacokinetic properties of the individual medication [3-7].

Initial reports on diazepam in pregnancy found a higher rate of cleft lip and palate with first trimester exposure [8]. Similarly, others have reported cleft palates, anal atresia, skeletal abnormalities, and "floppy baby" syndrome after delivery, although these adverse effects have not been confirmed by other investigative teams [9-11]. Benzodiazepine exposure in pregnancy has been associated with increased maternal age, tobacco use and lower education, which adds important potential confounders hindering the ability to isolate the impact of medication exposure [12]. Retrospective data shows women with benzodiazepine exposure have increased odds for preterm birth and low birth weight (<2500 g) [13]. However, when controlling for concurrent antidepressant use, the risk of preterm delivery was significantly attenuated [13]. In a subsequent study of a cohort of women with higher proportion of benzodiazepine exposure (n=85), the risk of preterm delivery remained significantly higher when controlling for additional psychotropic medication use [14].

Recent work by Freeman et al. found that benzodiazepine exposure (n=144) as reported across three time points (enrollment, seven months of gestation, and three months postpartum) significantly increased the risk of admission to NICU and small head circumferences [15]. A separate study evaluated the potential impact of maternal anxiety disorders, the authors found that maternal panic disorder (n=98) and generalized anxiety disorder (n=252) did not increase adverse outcomes. In contrast, benzodiazepine exposure (n=67) in pregnancy determined by maternal report at three times points (prior to 17 weeks' gestation, 28 (±2) weeks' gestation, and 8 (±4) weeks' postpartum) was associated with cesarean delivery, low birth weight, and use of ventilator support for newborns [16]. Our goal was to extend these previous studies in a prospective cohort of

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well characterized women with repeated documentation of exposures across the gestational period.

Current study objectives included: 1) evaluate the impact of benzodiazepine exposure on maternal and neonatal outcomes while evaluating potential interactive effects of psychiatric illness; and 2) determine the impact, if any, of gestational timing of benzodiazepine exposure and other exposures on these outcomes.

Materials and Methods

Study population and data collection

Pregnant women with neuropsychiatric illnesses referred to the Emory Women's Mental Health Program, a tertiary referral center for neuropsychiatric illness in pregnancy, were enrolled in a prospective, observational study of the impact of maternal stress, mental illness and pharmacologic exposures on pregnancy outcomes. Women were enrolled and provided informed consent prior to 16 weeks estimated gestation and followed through the first postnatal year. The study was approved by the Emory University Institutional Review Board and conducted between 1997 and 2012. Subjects were referred to the Women's Mental Health Program by primary care physicians, obstetric care providers, mental health care providers and self-referral. By design, the inclusion criteria for the primary investigation were broad, and only women with a currently active eating disorder or substance use disorder were excluded from participation.

Subjects were evaluated during pregnancy at 4 to 8 week intervals assessing stress, symptoms of depression and anxiety, and documentation of exposures (prescription, over the counter and environmental). Tracking sheets for all exposures (prescription, over the counter, environmental) were completed by clinician interview of subjects. At the initial pregnancy visit, exposure tracking sheets were completed from the estimated start of pregnancy based on the available indices of gestational age (based on last menstrual period) at the time of interview. Each subject was interviewed within 7 days after delivery to obtain information regarding labor and delivery including release of information for medical records. By convention, analyses were limited to the first pregnancy enrolled in the study for each subject for those women with multiple pregnancies over the duration of the study. The inclusion criteria for this current analysis included: (1) completed Structured Clinical Interview for the DSM-IV; (2) complete abstraction of obstetric and neonatal records; (3) documentation of medication exposure on a week-by-week basis across the entirety of gestation; and (4) singleton pregnancy to reduce potential confounds of multiple gestation on outcome measures.

Measures

Primary outcomes included: method of delivery (vaginal *versus* cesarean delivery), preterm birth (delivery that occurred at gestational age of more than 20 and before the completion of 37 weeks of gestation based on last menstrual period, yes/no), low infant weight (birth weight below 2500 grams, yes/no). Secondary and exploratory outcomes included infant major malformation (yes/no), Neonatal Intensive Care Unit (NICU) admission (yes/no), and special nursery care (yes/no). We chose to define benzodiazepine exposure a priori as a cumulative benzodiazepine exposure during pregnancy ≥ 2 weeks Women with benzodiazepine exposure less than two weeks' total were excluded from analyses e.g. not included in either benzodiazepine exposed or not exposed groups. This cumulative amount of benzodiazepine exposure was empirically selected to increase our confidence in separating exposed from non-exposed women for outcome analyses.

Statistical analysis

Bivariate analysis between benzodiazepine use, demographics and clinical characteristics were performed using chi-square independence test since all the variables were categorical. To examine the associations between benzodiazepine use and maternal and neonatal outcomes at delivery adjusting for covariates, logistic regression models were constructed using benzodiazepine as a dichotomized variable (yes/no) and as a continuous variable (weeks of exposure). Covariates included demographics, which included age groups (<30, 30-<35, 35-<40, >40), race (Caucasian *vs* other), marital status (married *vs* non-married), and education levels (≤ 13 years, 14-15 years, 16 years and >16 years), maternal obstetrical history including gravidity, planned pregnancy (yes/no), primiparous state (yes/no), delivery anesthesia (yes/no), lifetime maternal psychiatric diagnoses including Major Depressive Disorder (yes/no), Bipolar Disorder (yes/no), anxiety disorder (yes/no), Posttraumatic Stress Disorder (yes/no), history of substance use disorder (yes/no), and maternal exposures including yes or no for the current use of tobacco, antidepressant, and/or mood stabilizers (including Lithium, anti-epileptic drugs, and atypical antipsychotics). Age was changed to a categorical variable due to its non-linear relationships with most of the outcomes.

Since three of the covariates (planned pregnancy, delivery anesthesia, and current tobacco use) had the most missing values compared to the rest (about 2-4%), these three variables were included in each of the models only if the p values in the bivariate analysis between these and benzodiazepine use or each outcome were less than or equal to 0.2. The remaining covariates were included in all the models. The interactions between benzodiazepine use and covariates were also examined and included if $p < 0.05$. SAS 9.4 was used for all analyses.

Results

The original parent study included 1,359 pregnancies. A total of 633 women fulfilled inclusion criteria for the present analyses with 133 (21.0%) of the women classified as benzodiazepine exposed (Figure 1). The primary reasons for exclusion included incomplete records (including psychiatric diagnostic interview, tracking sheets for exposure, and obstetrical and/or neonatal records) in 553 pregnancies. A total of 27 women were excluded due to multiple gestation and 131 pregnancies were excluded from mothers with more than one pregnancy during the study. 15 women were excluded with acute benzodiazepine exposure (i.e. less than 2 weeks' duration of use during entire pregnancy).

The subjects in the cohort were a relatively homogenous group of women with regard to a high education level and 100% received prenatal care. The mean age of participants was 33.0±4.9 years and 87.5% were White, 7.4% African American, 2.2% Asian and 1.4% Native American with remaining identifying as Pacific Islander or multiple. A total of 2.7% identified as Hispanic ethnicity. The mean education was 16.0 (±2.1 years) and 82.9% were married. The majority

Table 1: Bivariate analysis between benzodiazepines use and demographics and clinical characters.

Variable	Benzodiazepine use, %		Total,% (n=633)
	No (n=500)	Yes (n=133)	
Maternal Demographics			
Age			
<30	26	22.6	25.3
30-<35	38.4	37.6	38.2
35-<40	28.8	31.6	29.4
40+	6.8	8.3	7.1
Caucasian	88.2	85	87.5
Married	83.6	80.5	82.9
Education*			
<=13 years	7.8	19.6	10.3
14-15 years	16.9	24.8	18.5
16 years	37.6	29.3	35.8
>16 years	37.8	26.3	35.3
Maternal Obstetrical History			
Gravidity			
1	35.9	31.8	35.1
2	34.1	28	32.9
3	12.9	17.4	13.8
>=4	17.1	22.7	18.3
Planned pregnancy	68.6	65.6	68
Primiparous	53	53	53
Delivery anesthesia	92.7	93	92.8
Lifetime Maternal Psychiatric Diagnoses			
Major Depressive Disorder	64.6	58.7	63.4
Bipolar Disorder*	21.2	30.8	23.2
Anxiety Disorder*†	47.4	68.4	51.8
Post-Traumatic Stress Disorder	18.4	21.8	19.2
Substance Use Disorder	49	57.1	50.7
Maternal Exposures			
Current Tobacco Use*	13.3	21.7	15.1
Current use of Antidepressant	72.8	78.2	73.9
Current use of Mood Stabilizer*	27.6	43.5	30.9
Maternal and Neonatal Outcomes			
Cesarean Section Delivery*	33.8	43.6	35.9
Preterm Delivery*	11	19.6	12.8
Low infant weight < 2500 grams*	5	9.8	6
Infant Malformation	2.8	4	3
Infant NICU admission	11	17.8	12.4
Infant special nursery requirement	13.6	17.1	14.3

*p<.05

†Including generalized anxiety disorder, panic disorder, social anxiety disorder and anxiety nos.

NICU; Neonatal Intensive Care Unit

fulfilled DSM-IV criteria for lifetime history of major depressive disorder (63.4%) per structured interview and 73.9% reported taking an antidepressant and 30.9% a mood stabilizer at some point during the pregnancy. The majority of women were primiparous (53.0%) and approximately one-third of subjects (32.0%) reported the current pregnancy as unplanned. Within the benzodiazepine exposed group (n=133), the most commonly prescribed benzodiazepines included lorazepam (46.6%), clonazepam (39.1%) and alprazolam (12.0%).

Table 1 shows the bivariate analysis results including demographics, psychiatric history, obstetrical history, and pregnancy outcomes. There were no statistical differences in age, race, or marital status between women with and without benzodiazepine exposure. Women with lower levels of education were more likely to have benzodiazepine exposure (p<0.0001). The mean gestational age at delivery was 38.6 weeks (SD=1.8). The benzodiazepine exposed group had higher rates of preterm delivery (19.6% *vs* 11.0%, p=0.01), operative delivery (43.6% *vs* 33.8%, p=0.04), low birth weight infants (9.8% *vs* 5.0%, p=0.04), and NICU admission (17.8% *vs* 11.0%, p=0.04). Women who met DSM-IV criteria for an anxiety disorder (including generalized anxiety disorder, panic disorder, social anxiety disorder or anxiety nos) (68.4% *vs* 47.4%, p <0.0001) and/or bipolar disorder (30.8% *vs* 21.2%, p=0.02) were more likely to take a benzodiazepine. Women taking a mood stabilizer were significantly more likely to have benzodiazepine exposure (p=<0.05), while no significant differences were found for antidepressant exposure. Women taking benzodiazepines were more likely to self-report tobacco use (21.7% *vs* 13.3%, p=0.02).

There were no statistical differences in gravidity, parity, method of delivery, infant malformation, or infant special nursery care between benzodiazepine exposed and non-exposed groups on initial bivariate analysis.

Parameter estimates from logistic regression models examining benzodiazepine effects on maternal and neonatal outcomes are included in Appendix 1. Odds ratios of benzodiazepine use for maternal and neonatal outcomes are presented in Table 2. The model for low birth weight revealed a significant interaction effect between concurrent use of benzodiazepine and tobacco. Specifically, for those with tobacco use, odds of low birth weight was six times higher in women taking benzodiazepine compared to those without BZD use (OR=6.88, CI 1.44-32.75). The impact of benzodiazepine use on low birth weight was not seen in the non-tobacco use groups. For the cesarean section delivery model, women with benzodiazepine use had three times higher odds of cesarean section delivery than those without benzodiazepine use if they were not diagnosed with post-traumatic stress disorder (OR=3.12, 95% CI 1.64- 5.94). This was not seen in women with post-traumatic stress disorder diagnosis. Even though the interaction between benzodiazepine use and tobacco use in this model was significant, the benzodiazepine effect was not significant regardless of tobacco use although a positive trend was shown between benzodiazepine use and cesarean section delivery for those women with tobacco use. Women with benzodiazepine use were also found to be more likely to have preterm delivery if their pregnancy was not planned (OR=3.69, 95% CI 1.40–9.71) and were more likely to require special nursery care following delivery if they

Table 2: Odds ratios of maternal and neonatal outcomes for benzodiazepine use. OR (95% CI).

	Cesarean section delivery	Preterm Delivery, < 37 weeks gestation	Low birth weight, <2500 grams	Infant Major Malformation	Infant Neonatal Intensive Care Unit	Infant Special Nursery Required
Benzodiazepine Use (yes *vs* no)				1.74 (0.51-5.96)	1.31 (0.72-2.41)	
No tobacco use	0.63 (0.31-1.24)		0.71 (0.22-2.22)			
With tobacco use	2.62 (0.87- 7.83)		6.88 (1.44-32.75)			
With no PTSD diagnosis	3.12 (1.64- 5.94)					
With PTSD diagnosis	0.52 (0. 17- 1.65)					
With planned pregnancy		1.18 (0.55- 2.52)				
With unplanned pregnancy		3.69 (1.40- 9.71)				
With male newborn						1.27 (0.68- 2.34)
With female newborn						2.61 (1.11- 6.13)

PTSD; Posttraumatic Stress Disorder

had female neonates (OR=2.61, 95% CI 1.11-6.13).

Gestational timing of exposure

Benzodiazepine use was also explored by use in either the first trimester only (0-13 weeks based on last menstrual period) (n=98), in the third trimester (≥ 28 weeks) only (n=69), and as a continuous exposure. The first and last trimesters were chosen as they are often associated with risk of infant malformation and postnatal effects, respectively. The average duration of benzodiazepine exposure was 20.0±14.2 weeks with forty women having exposure for 30 weeks or greater during gestation. Those with benzodiazepine exposure either in the first or third trimesters only were more likely to have preterm delivery (22% *vs* 11%).

Among all women there were a total of 18 known malformations (3%) present with five being in the benzodiazepine exposed group and associated with a longer duration of benzodiazepine use in pregnancy (parameter estimate = 0.05, p-value=0.02). Four out of the five malformations in the benzodiazepine exposed group were documented and had not been previously associated with BZD exposure including Tetralogy of Fallot, mild craniofacial dysmorphism, congenital kidney malformation, and atrial septal defect/patent foramen ovale. These findings were not significant when comparing first to third trimester exposure.

Discussion and Conclusion

The current study provided prospective data that underscores the difficulties in isolating the impact of benzodiazepine exposure in pregnancy as our estimated impact of benzodiazepine on maternal and neonatal outcomes had significant interaction effects with other factors. Approximately 1 out of 5 women reported benzodiazepine use for greater than 2 weeks during pregnancy. In contrast to previous reports, [12-14] the rate of adverse outcomes in this prospective cohort were modest. The rate of preterm delivery (<37 weeks' gestation based on last menstrual period) in our benzodiazepine exposed sample was 19.5%, which is higher than the national average (9.57%); [17] however, comparable to a recent report [18] in a similar population (17.9%). Similarly, rate of low birth weight infants (<2,500 gm) was approximately 9.7%, which is lower than the 16.4% reported by Yonkers and colleagues (2017) and more consistent with the national average (8.0%) [17].

These current analyses suggest that tobacco use in combination with benzodiazepine may be driving negative outcomes. Yonkers et al (2017) prospectively examined a cohort of 2,654 pregnant women with similar sociodemographic characteristics to our population examining exposure to psychotropic medications (11.0% serotonin-reuptake inhibitors, 2.5% benzodiazepine exposed (n=67).18 Data was gathered at three time points *via* phone interview at prior to 17 weeks' gestation, 28 (±2) weeks' gestation, and 8 (±4) weeks postpartum with definition of exposure not clearly defined. In this previous report, neither panic disorder or generalized anxiety disorder were associated with negative outcomes and when controlling for other factors such as tobacco, heavy drinking, and illicit substance use benzodiazepine exposure was only significant for increase odds of cesarean delivery (2.45 95% CI 1.36-4.40). Both our study and this previous study included high rates of tobacco use at 13.3 and 14.7 %, respectively.18

We found that only those infants with concomitant tobacco use and benzodiazepine exposure were at increased risk of low birth weight. A strong association between tobacco use and low birth weight has been established in multiple studies [19,20]. Adults with psychiatric illness, specifically anxiety, are more likely to use tobacco [20] and are therefore at greater risk of multiple exposures. Considering these factors, pregnant women with benzodiazepine use may need additional educational emphasis regarding negative effects of tobacco use during pregnancy.

Psychiatric diagnosis, specifically post-traumatic stress disorder, had a significant interactive effect that seems protective against cesarean section deliveries. In this study, benzodiazepine use in women with post-traumatic stress disorder but no tobacco use was associated with lower likelihood of receiving a cesarean section and benzodiazepine use was associated with higher risk of cesarean deliveries if moms used tobacco use but without post-traumatic stress disorder suggesting further the negative outcomes of tobacco exposure in these high risk populations. Only women with self-reported unplanned pregnancies and benzodiazepine were at higher risk of preterm deliveries. Our sample did have lower number of unplanned pregnancies than the national average, which is likely indicative of the strength of the sample being well educated, having full prenatal care, and higher socioeconomic status, therefore reducing these potential confounds. Due to these factors, the elevated rate of preterm delivery in our sample is not well understood and warrants further attention.

The study has several potential limitations that warrant

discussion. The homogeneity of the population limits the ability to generalize these findings to other populations. However, the cohort is devoid of many of the psychosocial and socioeconomic factors that could impact outcome supporting our efforts to isolate the impact of benzodiazepines in the population most likely to receive a benzodiazepine. Exposure to benzodiazepine was based on maternal report, and while prospective documentation of exposures is more accurate than retrospective report in perinatal studies optimally prescription filling records and/or laboratory confirmation may have enhanced the accuracy of determining exposures [21]. There are always concerns of the impact of patient adherence to medication regimens or underreporting of medication use. The indication for benzodiazepine use and dose was also not consistently documented; however, exposure to medications is thought to be more prudent with dosing typically not correlating with outcomes. Outcomes are dependent on the accuracy of the medical record and individuals recording outcomes were not blinded to benzodiazepine exposure. The two-week duration of benzodiazepine use was chosen a priori, and it may be that changing the duration or mg equivalents to define exposure may have influenced the results. Further stratification of exposure by trimester could also be of importance.

In summary, the use of benzodiazepines in pregnancy has historically been discouraged. In this study, women with perinatal benzodiazepine use also had high rates of tobacco use, were less educated and more likely to have an anxiety disorder. The concurrent use of benzodiazepines and tobacco was associated with increased risk of low birth weight infants and cesarean delivery. The presence of post-traumatic stress disorder diagnosis seemed to be protective for cesarean delivery. These findings underscore the importance of examining concomitant exposures during the perinatal period, particularly tobacco. Focusing on the effects of concomitant exposures and treatment of nicotine use disorders during pregnancy is an area of further interest.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Emory University Institutional Review Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards".

References

1. Paulozzi LJ, Karin AM, Hockenberry JM. Vital signs: variation among states in prescribing of opioid pain relievers and benzodiazepines-United States, 2012. MMWR Morb Mortal Wkly Rep. 2012; 63: 563-568.
2. American College of Obstetrics and Gynecology ACOG Practice Bulletin No. 92: Use of Psychiatric Medications During Pregnancy and Lactation. Obstetrics & Gynecology. 2008; 111: 1001-1020.
3. Iqbal MM, Tanveer S, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatric Services. 2002; 53: 39-49.
4. Cree JE, Meyer J, Hailey DM. Diazepman in labour: its metabolism and effect on the clinical condition and thermogenesis of the newborn. Br Med J. 1973; 4: 251-255.
5. Gamble JAS, Moore J, Lamki H, Howard PJ. A study of plasma diazepam levels in mother and infant. BJOG: An International Journal of Obstetrics & Gynaecology. 1977; 84: 588-591.
6. McBride RJ, Dundee JW, Moore J, Toner W, Howard PJ. A study of the plasma concentrations of lorazepam in mother and neonate. British journal of anaesthesia.1979; 51: 971-978.
7. Oo CY, Kuhn RJ, Desai N, Wright CE, McNamara PJ. Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. British journal of clinical pharmacology. 1995; 40: 231-236.
8. Safra MJ, Oakley GP. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. The Lancet. 1975; 306: 478-480.
9. Eros E, Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of nitrazepam, medazepam, tofisopam, alprazolam and clonazepam treatment during pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2002; 101: 147-154.
10. Rosenberg L, Mitchell AA, Parsells JL, Pashayan H, Louik C, Shapiro S. Lack of relation of oral clefts to diazepam use during pregnancy. NEJM. 1983; 309: 1282-1285.
11. Dolovich LR, Addis A, Vaillancourt JR, Power JB, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ. 1998; 317: 839-843.
12. Wikner BN, Stiller CO, Bergman U, Asker C, Kallen B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiology and drug safety. 2007; 16: 1203-1210.
13. Wikner BN, Stiller CO, Kallen B, Asker C. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: maternal characteristics. Pharmacoepidemiology and drug safety. 2007; 16: 988-994.
14. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. American journal of obstetrics and gynecology. 2009; 201: 579-e1.
15. Freeman MP, Góez-Mogollón L, McInerney KA, Davies AC, Church, TR, Sosinsky, Z, et al. Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: results from a prospective registry of women with psychiatric disorders. General hospital psychiatry. 2018; 53: 73-79.
16. Ventura SJ, Hamilton BE, Mathews TJ, Chandra A. Trends and variations in smoking during pregnancy and low birth weight: evidence from the birth certificate. Pediatrics. 2003; 111: 1176-1180.
17. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. National vital statistics reports: from the Center for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2015; 64: 1-64.
18. Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS. Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy with Risk of Adverse Birth Outcomes. JAMA Psychiatry. 2017; 74: 1145-1152.
19. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization. 1987; 65: 663.
20. Morissette SB, Tull MT, Gulliver SB, Kamholz BW, Zimering RT. Anxiety, anxiety disorders, tobacco use, and nicotine: a critical review of interrelationships. Psychological bulletin. 2007; 133: 245.
21. Newport DJ, Brennan PA, Green P, Ilardi D, Whitfield TH, Morris N, et al. Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. BJOG: An International Journal of Obstetrics & Gynaecology. 2008; 115: 681-688.