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Use of vasoactive medications in pregnancy and the risk of stillbirth among birth defect cases

Stephen Kerr[1], **Dominique Heinke**[2], **Mahsa M. Yazdy**[2], **Allen A. Mitchell**[1], **Anne Marie Darling**[2], **Angela Lin**[2,3], **Eirini Nestoridi**[2], **Martha M. Werler**[4], **National Birth Defects Prevention Study**

[1]Slone Epidemiology Center, Boston University, Boston, Massachusetts, USA

[2]Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, Massachusetts, USA

[3]Medical Genetics Unit, Mass General Hospital for Children, Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Epidemiology, Boston University, Boston, Massachusetts, USA

Abstract

Background: Many previous studies have identified risk factors for stillbirth, but few examine stillbirth among pregnancies affected with birth defects. Because many hypothesized etiologies of stillbirth work through vascular pathologies of the placenta, we examined maternal use of vasoactive medications in relation to stillbirth among pregnancies affected with birth defects.

Methods: Data were analyzed from the National Birth Defects Prevention Study (1997–2011). We examined use of nonsteroidal anti-inflammatory drugs (NSAIDs), decongestants, short- or long-acting beta-agonists (SABA/LABA), and antihypertensive medications in relation to pregnancies affected by birth defects ending in stillbirth compared to live birth. Associations were measured with odds ratios (ORs) for early pregnancy use and hazard ratios (HRs) for time-varying late pregnancy use.

Results: Among all birth defects (n = 12,394), the risk of stillbirth was associated with use of antihypertensive medications in early (odds ratio [OR]: 1.8; 95% confidence interval [CI]: 1.0, 3.1) and late pregnancy (HR: 2.0; 95% CI: 1.1, 3.6). Other vasoactive medications were not associated with increased risk of stillbirth. Of 27 specific defect groups, increased risks were observed for only one medication/defect pair: early decongestant use was more common among mothers of stillbirth versus live birth cases with spina bifida (OR: 2.4; 95% CI: 0.9, 6.5).

Conclusion: This exploratory analysis of vasoactive medication use suggests that use of NSAIDs, decongestants, and SABA/LABA is not associated with increased risk of stillbirth

Correspondence Stephen Kerr, 72 East Concord Street, L-7, Boston, MA 02118. skerr1@bu.edu.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

CONFLICT OF INTERESTS

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among pregnancies affected with birth defects. Our finding of increased risks associated with antihypertensive medication use raises questions of confounding by indication, which we were not able to fully address.

Keywords

birth defects; pregnancy; stillbirth; vasoactive

1 | INTRODUCTION

Approximately 24,000 stillbirths occur in the United States each year (Hoyert & Gregory, 2016, 2020). While the prevalence of stillbirth is approximately 0.6% in the U.S. general population (MacDorman & Gregory, 2015), reported estimates range between 2.7% and 5.5% among pregnancies affected by birth defects overall (Frey et al., 2014; Groen et al., 2017; Heinke et al., 2020). These birth defects can be sufficiently serious to be considered causative; a 2020 CDC study listed birth defects as the cause of 10.8% of stillbirths (Hoyert & Gregory, 2020). Birth defects most commonly found among stillbirths include lethal malformations like limb–body wall complex (LBWC), anencephaly or bilateral renal agenesis, with reported stillbirth risk for LBWC as high as 49% (Heinke et al., 2020). But even fetuses with isolated birth defects which do not involve vital organs, like cleft palate, are at risk of stillbirth two to nine times that in the general population (Heinke et al., 2020), implying that this elevated stillbirth risk is not necessarily due to the defect itself.

Although the presence of a birth defect is a risk factor for stillbirth, there is relatively little known about additional stillbirth risk factors *among pregnancies with birth defects* (Frey et al., 2014; Heinke et al., 2020). Identifying modifiable factors associated with stillbirth could potentially increase survival to live birth for these already susceptible pregnancies.

Etiology of stillbirth is varied and often unknown; however, many identified and hypothesized causes work through vascular pathologies of the placenta. These can include maldevelopment, obstruction, or loss of integrity of either maternal or fetal vascular supply (Redline, 2008), leading to growth restriction and potentially fetal death. Adverse fetal outcomes, including perinatal death, are more common among mothers with chronic hypertension (Bramham et al., 2014; Zetterström, Lindeberg, Haglund, & Hanson, 2008). Medications that affect maternal/fetal vasculature may increase the risk of stillbirth overall (Lennestål, Otterblad Olausson, & Källén, 2009), but especially so for fetuses already vulnerable to stillbirth due to the presence of a birth defect.

We sought to examine antenatal exposure to medications with vasoactive properties and the risk of stillbirth among birth defect cases in the National Birth Defects Prevention Study (NBDPS), which includes liveborn and stillborn cases with selected major birth defects.

2 | METHODS

The NBDPS is a large, multistate case–control study of birth defects that was conducted from 1997–2011. Its methods have been described in detail previously (Reefhuis et al., 2015). Briefly, the NBDPS used active state birth defects surveillance programs to recruit

completed pregnancies with selected identified birth defects as cases and random samples of live births without birth defects as controls from the same geographic areas at 10 study centers across the United States. Although cases could be live births, stillbirths, or terminations, all control infants were liveborn. Between 6 weeks and 24 months after the estimated delivery date, eligible women who agreed to participate were administered a computer-assisted telephone interview eliciting responses on various factors related to sociodemographic factors, health, and pregnancy history, including detailed information on exposures to medications during pregnancy, which included both prescription and over-the-counter (OTC) medications.

2.1 | Outcomes

As our objective was to investigate potentially modifiable risk factors among fetuses with birth defects, this analysis was limited to case infants where the pregnancy outcome was either a live birth or stillbirth. We further limited the study population based on previous work on stillbirth risk in NBDPS (Heinke et al., 2020). Heinke et al. (2020) described certain birth defects frequently diagnosed based only on postnatal findings, or otherwise unlikely to be diagnosed consistently in stillbirths. We, therefore, considered ineligible the following malformations: biliary, small intestinal, colonic or anorectal atresia, craniosynostosis, cerebellar hypoplasia, hypospadias, glaucoma, cataracts, choanal atresia, limb deficiency not otherwise stated, and all isolated heart defects. The main outcome of interest was stillbirth risk among all eligible birth defect cases combined. We also examined stillbirth risk for specific birth defects where sample size allowed. Table S1 presents the prevalence of stillbirth and live birth according to specific birth defect.

2.2 | Exposures

We examined four separate vasoactive medication groups for this analysis: nonsteroidal anti-inflammatory drugs (NSAIDs), decongestants, short- or long-acting beta-agonists (SABA/LABA), and antihypertensive medications. For the first three groups, where sample size allowed, we also examined the following specific medications within these groups: ibuprofen, aspirin, naproxen (NSAIDs); pseudoephedrine (decongestants), and albuterol (SABA/LABA). The antihypertensive group consisted of angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, thiazides, or “other” vasodilator/antihypertensive medications (e.g., methyldopa, “antihypertensive not otherwise specified”), each of which did not include sufficient numbers to permit risk estimation individually. Antimigraine medications (ergot alkaloids, triptans), anorexiants, and nitrates have vasoactive properties, but were not analyzed due to small numbers of exposed cases.

2.3 | Analysis

The covariates obtained from the interview and included in this analysis included demographic factors (maternal race/ethnicity, age, education, prepregnancy body mass index, country of birth, language of interview), pregnancy history factors (parity, gravidity, history of stillbirth, termination, miscarriage, tubal or molar pregnancies), and information on the most recent pregnancy (intention, timing of prenatal care, fertility medications, multiple gestation, infant sex, and year of due date). We also included data on maternal

characteristics such as smoking and alcohol use. Maternal health factors examined included: injuries during pregnancy, history of diabetes mellitus, high blood pressure, seizures, kidney, bladder or urinary tract infections during pregnancy, and state study site. High blood pressure (HBP) was categorized as: HBP in the index pregnancy; a history of HBP, but no HBP in the index pregnancy; and never diagnosed with HBP. Diabetes mellitus history was categorized as: nondiabetic; pre-existing Type 1 or Type 2 diabetes; pre-existing gestational diabetes; Type 1 or Type 2 diabetes during index pregnancy; gestational diabetes during index pregnancy.

Because stillbirth is defined as a fetal loss occurring during or after the 20th week of pregnancy, we examined two distinct windows of exposure during pregnancy: early pregnancy (exposures reported from the month prior to pregnancy [B1] through Day 139 of gestation) and late pregnancy (exposures reported from Day 140 through end of pregnancy). The reference group was live births or stillbirths with no exposure from B1 through the end of pregnancy.

Analyzing these two windows required two separate approaches. Since by definition stillbirth cannot occur before Day 140, early pregnancy exposures occurring before Day 140 were analyzed using logistic regression comparing exposure in this window between live births and stillbirths. We calculated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for early pregnancy exposures, when there were four or more exposed stillbirth cases. The reference group was live births or stillbirths with no exposure from B1 through the end of pregnancy.

For exposures occurring between Day 140 and the end of pregnancy, we took into consideration the likelihood of longer gestations and therefore greater opportunity for exposure among live births than among stillbirths. This issue is especially apparent for antihypertensives as gestational hypertension/preeclampsia become more common as the pregnancy nears term. This potential for bias in observational studies of pregnancy has been described previously (Hutcheon, Kuret, Joseph, Sabr, & Lim, 2013; Matok, Azoulay, Yin, & Suissa, 2014). We, therefore, analyzed late pregnancy exposures by calculating crude and adjusted hazard ratios (HRs), with gestational length in days as the time-scale and stillbirth as the event, censoring at live birth, and presenting risk estimates when there were four or more exposed cases. We characterized medication exposure as time-varying, allowing exposure status to switch between exposed and unexposed. As an example, a mother who reported ibuprofen use only from Day 150 to Day 156 would contribute unexposed person time for the first 10 days of followup after Day 140, exposed person time for the next 7, and then unexposed again until the end of pregnancy. We tested the proportional hazard assumption through a correlation test between the weighted Schoenfeld residuals and failure times.

We also considered three sensitivity analyses. First, maternal interviews were conducted up to 2 years after the estimated date of delivery; for medications that are taken intermittently (e.g., over-the-counter NSAIDs), women may report with both vague frequency (e.g., taken “as needed anytime in pregnancy”) or vague duration (e.g., “for a week at some point during the second half of pregnancy”). Thus, substantial misclassification of exposure could occur

when a short duration of use (e.g., 7 days duration) is reported along with a wide window of exposure (e.g., September 1st–December 31st = 120 days). We, therefore, re-ran all analyses excluding any exposures reported “as needed” or reported with a duration of use shorter than the dates given for the window of exposure.

Next, to isolate effects of early versus late exposures, we excluded those that overlapped early and late pregnancy. Finally, certain specific birth defects are disproportionately represented among stillbirths (i.e., anencephaly, amniotic bands with limb–body wall complex, bilateral renal agenesis). Thus, in a third sensitivity analysis, in order to concentrate more specifically on potentially preventable stillbirths, we excluded these birth defects to focus estimates on defects with higher livebirth probabilities.

Although we examined risk of stillbirth among all included birth defect cases as the main outcome, in a supplementary analysis we examined the risk of stillbirth for specific birth defects, where sample size allowed. Further, our results for antihypertensive medication use led to a post-hoc examination of stillbirth risk as related to antihypertensive use and reported history of high blood pressure.

3 | RESULTS

There were 32,200 cases with birth defects available for analyses; among these, we excluded 711 that ended in an outcome other than live- or stillbirth (termination [n = 689], fetal death less than 20 weeks (n = 4), or missing/not stated [n = 18]). We also excluded 2,039 liveborn cases recruited from study centers that did not recruit stillbirths (New Jersey; New York, 1997–1999). Also excluded were 16,802 cases with ineligible birth defects due to diagnosis most likely dependent on postnatal findings. Finally, we excluded those with missing or implausible gestational age (n = 40, 20 live births and 20 stillbirths), and those subjects who did not complete the medication exposure questions (n = 214). This left a final study population of 12,394 birth defect case subjects: 448 stillbirths and 11,946 live births (see Figure 1).

Characteristics of stillborn and liveborn cases are shown in Table 1. Mothers of stillbirths and live births with birth defects were generally similar. Mothers of stillbirths cases were more likely to be non-Hispanic Black or Hispanic, be less than 20 years old, have lower education, be born outside the United States, be Spanish speaking, primiparous, have a previous stillbirth, not have prenatal care, not drink alcohol, to have Type 1 or 2 diabetes, or have a kidney, bladder, or urinary tract infection in early pregnancy. Stillborn cases were more likely than live births to be female sex, and differences in stillbirth prevalence also existed by study center.

3.1 | Nonsteroidal anti-inflammatory drugs

Characteristics of exposure among live births are given in Table 2. In early pregnancy, NSAID use was more common among non-Hispanic White, older, and more educated women, as well as those reporting fertility treatments, smoking, drinking alcohol, an injury in the first trimester, and high blood pressure. Use was highest in Massachusetts and lowest

in Texas and appeared to increase over the years of the study. Use was less common in women who reported four or more previous live births or reported no prenatal care.

In late pregnancy, NSAID use was more common among mothers who were of non-Hispanic Black race/ethnicity, had four or more pregnancies, had a previous stillbirth or tubal pregnancy, did not plan the index pregnancy, had no prenatal care, were smokers, and reported a kidney/bladder or UTI in late pregnancy. Late pregnancy use was highest in Arkansas, and lowest in Massachusetts. Late pregnancy use was less common among those of Hispanic race/ethnicity and those with college education. For both windows of exposure, foreign-born and Spanish-speaking women were less likely to report use.

3.2 | Decongestants

In both early and late pregnancy, decongestant use was most common in non-Hispanic White, higher educated women, and alcohol drinkers, and least common in Hispanic, young, foreign-born, and Spanish-speaking women and those reporting four or more previous live births. In both windows, use also appeared to decrease over time and was lowest in California.

3.3 | Short- or long-acting beta-agonists

In both windows, SABA/LABA use was more common in those with obesity, those with a previous tubal or molar pregnancy, smokers, those reporting injury during pregnancy, those reporting high blood pressure, and those reporting seizures. Use was highest in New York and lowest in Texas. Use was less common in Hispanic women, foreign-born, Spanish speakers, those with four or more previous live births, and those without prenatal care. Early SABA/LABA use was more common in those of “other” race/ethnicity, unplanned pregnancies, and those with pre-existing diabetes. Late pregnancy use was more common in those with a previous miscarriage, and decreased slightly over time.

3.4 | Antihypertensive medications

In both windows, antihypertensive use was more common in non-Hispanic Black women, those who were older, and those who were obese. As expected, use was very common among those reporting a diagnosis of high blood pressure, but use was also common in those who reported fertility treatments or diabetes. Use was most common in North Carolina and increased over time. Exposure was less common in foreign-born, Spanish speakers, and those without prenatal care. Those with a previous stillbirth were more likely than those without to report exposure in late pregnancy but not early pregnancy.

There were insufficient exposures among stillbirth cases to examine specific antihypertensive medications; however, among liveborn cases, the most commonly reported medications were methyldopa, antihypertensive NOS (not otherwise specified), the calcium channel blocker nifedipine, the beta-blockers labetalol and atenolol, and the ACE inhibitor lisinopril.

3.5 | Risk estimates: early pregnancy exposures

Results for early pregnancy exposures can be found in Table 3. Early pregnancy exposure did not materially differ between stillbirth and live birth cases for NSAIDs (33.6% of stillbirths and 35.5% of live births), decongestants (8.3% and 9.2%, respectively), and SABA/LABAs (3.6% and 4.0%, respectively). Exposure to antihypertensive medications in early pregnancy was more common for stillbirth cases than live birth cases (3.2% vs. 1.8%; crude OR [95% CI] = 1.8 [1.0, 3.1]). For all analyses, adjustment for potential confounders did not change risk estimates by more than 10%, so crude odds ratios are presented.

Risk estimates for specific medications were generally similar to risk estimates for the larger drug groups, although among NSAIDs, risk was slightly lower for aspirin exposure: 0.7(0.4, 1.1), and slightly higher for naproxen exposure: 1.2(0.8, 1.8). Results of sensitivity analyses can be found in Table S2. Among live births, vague or “as needed” medication exposure reports ranged from roughly 4% of antihypertensive exposures to 14% of NSAIDs. Exclusion of these exposures did not materially change risk estimates. Limiting exposures to those occurring only in early pregnancy also resulted in risk estimates that were largely similar to the main analysis. Exclusion of high mortality malformations resulted in largely similar risk estimates; the largest shift for SABA/LABA use: increasing slightly from 0.9 (0.5, 1.5) in the main analysis to 1.2 (0.7, 2.2).

3.6 | Risk estimates: late pregnancy exposures

Comparison of late pregnancy exposures can be found in Table 4. Exposure prevalence did not materially differ between stillbirth and live birth cases for NSAIDs (17.5% of stillbirths and 16.0% of live births) and SABA/LABAs (3.8% of stillbirths and 4.6% of live births). Use of decongestants was less common in stillbirths (2.2%) compared to live births (5.3%). Antihypertensive medications were more commonly used among stillbirths (3.4%) than live births (2.3%). For all analyses, adjustment for potential confounders did not change risk estimates by more than 10%, so crude HRs are presented.

The crude risk estimate for late pregnancy NSAID use approximated the null (0.9 [0.6, 1.3]), and for decongestant use, it was 0.6 (0.2, 1.9). The crude HR for SABA/LABA use was 0.7 (0.3, 1.3), and for antihypertensive use, it was elevated at 2.0 (1.1, 3.6). We found no evidence of violation of the proportional hazard assumption in these models, with p values ranging from .4981 for late pregnancy antihypertensive exposure to .9545 for late pregnancy decongestant exposure. There was little variation in risk when specific medications were examined. Among sensitivity analyses, exclusion of “as needed” use (ranging among live births from 3% of antihypertensive exposures to 19% of NSAID exposures) did not materially change estimates. Limiting exposures to those that occurred only in late pregnancy resulted in slightly higher point estimates for NSAIDs and ibuprofen, although CIs were wide: (1.3 [0.3, 5.3] for NSAIDs and 1.7 [0.4, 6.7] for ibuprofen). The sensitivity analysis excluding highly lethal malformations resulted in risk estimates that were largely similar to the main analysis (see Table S3).

3.7 | Specific malformations

Although power was limited, we were able to calculate risk estimates among some specific malformations (see Tables S4a–4d). Of the 243 potential comparisons in each time window (27 specific malformations and 8 drug groups), we were able to calculate risk estimates for 33 of these in early pregnancy (14%) and 13 in late pregnancy (5%). Of these 33 early pregnancy exposures, risk estimates ranged from 0.4 (0.2, 0.9) for any NSAID exposure and stillbirth among gastroschisis cases to 2.8 (1.0, 7.7) for pseudoephedrine exposure and stillbirth among spina bifida cases. The 13 HRs calculated for late pregnancy exposure among specific malformations ranged from 0.2 (0.0, 1.5) for NSAID exposure and stillbirth among gastroschisis cases to 2.3 (0.7, 8.2) for ibuprofen and stillbirth among cleft palate cases.

3.8 | Further analysis

We attempted to further investigate the positive associations with antihypertensive medications by stratifying use according to history of high blood pressure diagnosis. These results are found in Table S5. Although power was limited, compared to unexposed subjects without a prior diagnosis of high blood pressure, risk estimates approximated the null for those reporting a previous diagnosis but no antihypertensive medication exposure. Estimates were highest among those exposed to antihypertensive medications who reported a previous diagnosis but no high blood pressure during the index pregnancy: for early pregnancy exposure OR = 2.9 (1.0, 8.1); for late pregnancy exposure HR = 3.3 (1.0, 10.3). Risk estimates were also elevated for those exposed to antihypertensive medications and with high blood pressure reported in the current pregnancy: OR for early pregnancy exposure = 1.9 (1.0, 3.8); HR for late pregnancy exposure = 1.9 (0.9, 3.8).

4 | DISCUSSION

Examining birth defect cases in the NBDPS, we found relatively null associations between stillbirth and three commonly-used classes of medications with vasoactive properties. The one class for which we identified elevated risk estimates, antihypertensive medications, includes medications used to treat a condition that previous research has consistently identified as a stillbirth risk (Flenady et al., 2011). Although this study was confined to stillbirth risk among fetuses with birth defects and is not generalizable to all pregnancies, our observed positive association for antihypertensive medications is similar to what has been reported for overall stillbirth risk in other studies (Buawangpong, Teekachunhatean, & Koonrungsesomboon, 2020). Our data show that among birth defect cases, stillbirths were approximately twice as likely as live births to have been exposed to antihypertensive medication. If this effect is real, more intensive monitoring of fetal well-being among women with a prenatal diagnosis of a structural birth defect and underlying hypertension and/or use of antihypertensive medications may be warranted (Driggers, Bryant, & Ghidini, 2021).

It is difficult to disentangle the potential effect of medications from the effects of the underlying illness, and this is particularly problematic for antihypertensive medications. Although NBDPS does not consistently capture indication for use, it is relatively rare that

antihypertensive drugs would be taken in the absence of a high blood pressure diagnosis; roughly 80% of those exposed report a diagnosis. (Among those without a diagnosis, exposures in early pregnancy were mainly to beta-blockers, diuretics, and ACE inhibitors, and in late pregnancy to calcium channel blockers to stop labor). However, stillbirth prevalence was not elevated among those who reported a high blood pressure diagnosis prior to or during the index pregnancy but no antihypertensive treatment in the index pregnancy. Although this result may point to the medication as the more likely causal agent, we have no data on blood pressure levels during pregnancy, blood pressure screening, or severity of illness. Disease that requires medication is likely more severe than disease that is untreated or treated non-pharmacologically; however, the available data did not allow satisfactory exploration of these issues.

Although we attempted to distinguish those with HBP in the index pregnancy from those without, the interview questions did not provide a path to more meaningful group definitions. We recognize that women whose blood pressure was controlled by medication might not have considered themselves to have had high blood pressure during pregnancy. Further, the interview also did not allow us to distinguish chronic hypertension from pregnancy-related HBP, or more clearly characterize disease based on blood pressure control, or screening.

There are a number of strengths of this analysis. It is one of the few analyses to examine risk for stillbirth among pregnancies with a malformation. We used a large population-based study, and accounted for time-varying exposure to limit potential bias due to a time-varying indication for treatment.

There are also several limitations. The NBDPS was not designed to investigate stillbirth risk, so ascertainment biases are possible. This may be reflected in the varied stillbirth ascertainment rate by study center (ranging from 0.8% of cases in New York to 5.1% of cases in California); however, we do not think this variation would be related to exposure status. We excluded induced abortions, and it is unclear how this competing risk for stillbirth may influence these pathways. However, the malformations disproportionately represented among stillbirths that were excluded from the third sensitivity analysis also have high rates of termination (Schechtman, Gray, Baty, & Rothman, 2002). This sensitivity analysis resulted in largely similar risk estimates. This dataset also does not capture precise intrauterine date of fetal death; we instead measured pregnancy length as the number of days between last menstrual period and delivery. It is possible that we included exposures that occurred after the date of fetal death but prior to delivery. However, between 80% and 90% of women will undergo spontaneous labor within 1–2 weeks of diagnosis of the stillbirth (Chakhtoura & Reddy, 2015).

Additionally, we had insufficient power to examine drug-specific malformation-specific risks, and in the case of antihypertensives, therapeutic class-specific risks. We recognize that pharmacologic action may vary across these subclasses but were unable to examine these in any detail. Sample size also prevented a more thorough examination of potential confounding, especially confounding by indication. Although we did not observe material confounding by measured factors, it remains possible that estimates are biased in either

direction by unmeasured confounders, which limits the generalizability of our findings. The lack of stillborns without birth defects in this analysis limits the generalizability of our findings. Our observations that exposure to NSAIDs, decongestants, and asthma medications do not increase the risk of stillbirth in the presence of a birth defect cannot be applied to all pregnancies.

Overall, we found relatively reassuring results that among birth defect cases, three commonly used types of medications (NSAIDs, decongestants, SABA/LABAs) are not associated with stillbirth. Results for antihypertensive medications confirm previous analyses showing hypertensive disorders as potential causes of stillbirth, and support the importance of vascular/placental pathways in stillbirth risk, independent of the risk conferred by the birth defect itself.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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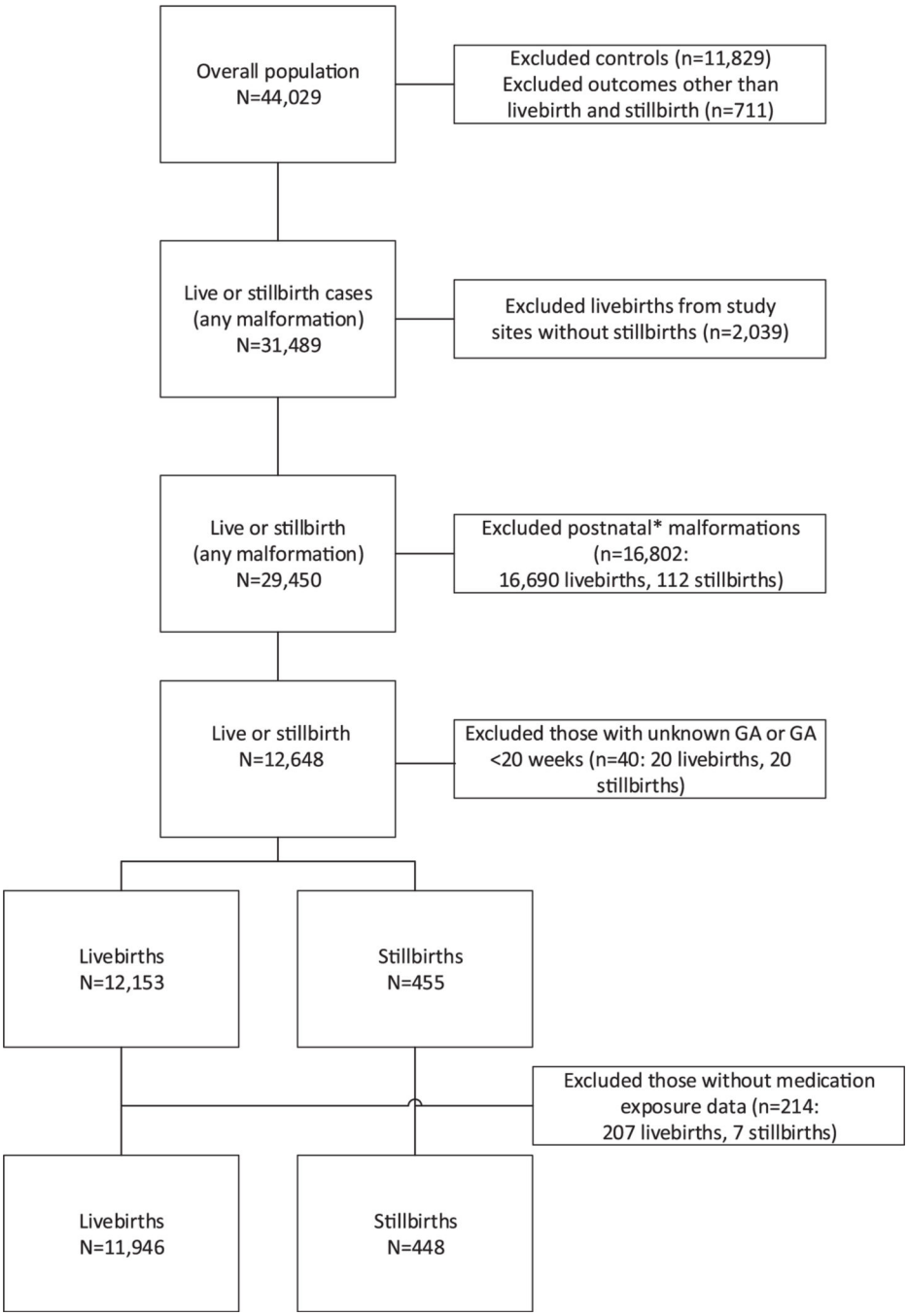

FIGURE 1.
Study population—National Birth Defects Prevention Study—1997–2011

TABLE 1

Characteristics of livebirths and stillbirths, among case subjects, National Birth Defects Prevention Study 1997–2011

Characteristic	Livebirths (*N* = 11,946) *N* (%)	Stillbirths[a] (*N* = 448) *N* (%)
Maternal race/ethnicity		
Non-Hispanic White	6,675 (55.9)	196 (43.8)
Non-Hispanic Black	1,005 (8.4)	62 (13.8)
Hispanic	3,452 (28.9)	156 (34.8)
Other	813 (6.8)	34 (7.6)
Maternal age at delivery		
<20 years old	1,562 (13.1)	78 (17.4)
20–24	3,160 (26.5)	117 (26.1)
25–29	3,140 (26.3)	125 (27.9)
30–34	2,561 (21.4)	73 (16.3)
35+	1,523 (12.7)	55 (12.3)
Maternal education		
<High school	2,434 (20.6)	118 (26.6)
High school	3,267 (27.7)	125 (28.2)
Some college	3,153 (26.7)	120 (27.1)
College+	2,940 (24.9)	80 (18.1)
Maternal BMI		
Underweight (<18.5)	670 (5.6)	20 (4.5)
Normal weight (18.5 ≤ BMI <25)	5,882 (49.2)	204 (45.5)
Overweight (25 ≤ BMI <30	2,553 (21.4)	104 (23.2)
Obese (≥30)	2,253 (18.9)	90 (20.1)
Missing information	588 (4.9)	30 (6.7)
Mother born in USA		
Yes	9,270 (77.6)	319 (71.2)
No	2,528 (21.2)	123 (27.5)
Missing information	148 (1.2)	6 (1.3)
Language of interview		
English	10,687 (89.5)	386 (86.2)

Characteristic	Livebirths (*N* = 11,946) *N* (%)	Stillbirths[a] (*N* = 448) *N* (%)
Spanish	1,184 (9.9)	58 (12.9)
Interview translated	75 (0.6)	4 (0.9)
Parity		
Zero previous livebirths	5,263 (44.1)	219 (48.9)
1 previous livebirth	3,552 (29.8)	103 (23.0)
2 previous livebirths	1873 (15.7)	66 (14.7)
3 previous livebirths	784 (6.6)	40 (8.9)
4+ previous livebirths	451 (3.8)	20 (4.5)
Gravidity		
Primiparous	3,811 (32.0)	162 (36.2)
1 previous pregnancy	3,325 (27.9)	108 (24.1)
2 previous pregnancies	2,196 (18.4)	76 (17.0)
3 previous pregnancies	1,277 (10.7)	50 (11.2)
4+ previous pregnancies	1,314 (11.0)	52 (11.6)
Previous stillbirth		
Yes	189 (1.6)	15 (3.3)
Previous abortion		
Yes	1,365 (11.4)	42 (9.4)
Previous miscarriage		
Yes	2,900 (24.3)	103 (23.0)
Previous tubal pregnancy		
Yes	167 (1.4)	4 (0.9)
Previous molar pregnancy		
Yes	48 (0.4)	1 (0.2)
Planned pregnancy		
Yes	6,576 (55.2)	244 (55.1)
Prenatal care		
No prenatal care	162 (1.4)	15 (3.5)
By end of P3	9,914 (85.9)	355 (83.1)
P4 or later	1,468 (12.7)	57 (13.3)
Any fertility medication or procedure		

Characteristic	Livebirths (*N* = 11,946) *N* (%)	Stillbirths[a] (*N* = 448) *N* (%)
Yes	644 (5.4)	22 (4.9)
Multiple birth		
Multiple	615 (5.2)	22 (4.9)
Year of due date		
1997–2001	3,149 (26.4)	119 (26.6)
2002–2006	4,281 (35.8)	166 (37.1)
2007–2011	4,516 (37.8)	163 (36.4)
Infant Sex		
Male	6,523 (54.7)	189 (44.1)
Female	5,405 (45.3)	240 (55.9)
Maternal smoking		
Any smoking between B1 and P3	2,613 (21.9)	83 (18.5)
No smoking between B1 and P3	9,228 (77.2)	361 (80.6)
Missing information	105 (0.9)	4 (0.9)
Maternal alcohol		
Any drinking between B1 and P3	4,280 (35.8)	127 (28.3)
No drinking between B1 and P3	7,532 (63.1)	315 (70.3)
Missing information	134 (1.1)	6 (1.3)
Any injury in B1-P3		
Yes	395 (3.5)	15 (3.5)
Any injury in P4-EOP		
Yes	601 (5.3)	18 (4.2)
Diabetes		
Nondiabetic	10,725 (90.8)	400 (89.9)
Pre-existing diabetes (Type 1 or 2)	268 (2.3)	15 (3.4)
Pre-existing gestational diabetes	234 (2.0)	11 (2.5)
Type 1 or 2 diabetes during index pregnancy	17 (0.1)	2 (0.4)
Gestational diabetes during index pregnancy	567 (4.8)	17 (3.8)
Ever told you had high blood pressure		
Yes	1750 (14.7)	64 (14.3)
Pregnancy-related HBP		

Characteristic	Livebirths (*N* = 11,946) *N* (%)	Stillbirths[a] (*N* = 448) *N* (%)
Never diagnosed with HBP	10,183 (85.3)	384 (85.7)
HBP not related to index pregnancy	582 (4.9)	25 (5.6)
HBP in index pregnancy	1,113 (9.3)	36 (8.0)
HBP diagnosed after delivery	55 (0.5)	3 (0.7)
Any kidney/bladder/UTI in B1-P3		
Yes	1,115 (9.4)	57 (12.9)
Any kidney/bladder/UTI in P4-EOP		
Yes	1,656 (13.9)	59 (13.3)
Have you ever had seizures?		
Yes	426 (3.6)	18 (4.0)
Site Id		
Arkansas	1,499 (12.5)	64 (14.3)
California	1989 (16.6)	107 (23.9)
Iowa	1,176 (9.8)	33 (7.4)
Massachusetts	1,457 (12.2)	30 (6.7)
New York	776 (6.5)	6 (1.3)
Texas	1,466 (12.3)	62 (13.8)
CDC/Atlanta	1,351 (11.3)	56 (12.5)
North Carolina	979 (8.2)	47 (10.5)
Utah	1,253 (10.5)	43 (9.6)
Any reported exposure to known teratogen		
Yes	18 (0.2)	1 (0.2)

Note. B1 = month before conception; BMI = body mass index; EOP = end of pregnancy; HBP = high blood pressure; P3 = third month of pregnancy; P4 = fourth month of pregnancy; UTI = urinary tract infection.

[a]Stillbirth, fetal death ≥20 wks.

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TABLE 2

Characteristics of vasoactive medication exposure among live born case subjects, National Birth Defects Prevention Study 1997–2011

	Any NSAID		Any decongestant		Any SABA/LABA		Any antihypertensive	
Characteristic	**Early pregnancy *N* = 4,096 (34.3%)**	**Late pregnancy *N* = 1,412 (11.8%)**	**Early pregnancy *N* = 1,055 (8.8%)**	**Late pregnancy *N* = 583 (4.9%)**	**Early pregnancy *N* = 471 (3.9%)**	**Late pregnancy *N* = 546 (4.6%)**	**Early pregnancy *N* = 212 (1.8%)**	**Late pregnancy *N* = 277 (2.3%)**
Maternal race/ethnicity								
Non-Hispanic White	2,699 (40.4)	840 (12.6)	752 (11.3)	418 (6.3)	307 (4.6)	361 (5.4)	115 (1.7)	161 (2.4)
Non-Hispanic Black	355 (35.3)	160 (15.9)	73 (7.3)	39 (3.9)	49 (4.9)	48 (4.8)	35 (3.5)	47 (4.7)
Hispanic	789 (22.9)	312 (9.0)	172 (5.0)	102 (3.0)	63 (1.8)	81 (2.3)	43 (1.2)	49 (1.4)
Other	252 (31.0)	100 (12.3)	58 (7.1)	24 (3.0)	52 (6.4)	56 (6.9)	19 (2.3)	20 (2.5)
Maternal age at delivery								
<20 years old	508 (32.5)	236 (15.1)	71 (4.5)	34 (2.2)	56 (3.6)	66 (4.2)	7 (0.4)	15 (1.0)
20–24	1,049 (33.2)	414 (13.1)	249 (7.9)	158 (5.0)	134 (4.2)	145 (4.6)	26 (0.8)	46 (1.5)
25–29	1,050 (33.4)	327 (10.4)	322 (10.3)	177 (5.6)	123 (3.9)	147 (4.7)	50 (1.6)	70 (2.2)
30–34	919 (35.9)	261 (10.2)	275 (10.7)	132 (5.2)	107 (4.2)	129 (5.0)	58 (2.3)	71 (2.8)
35+	570 (37.4)	174 (11.4)	138 (9.1)	82 (5.4)	51 (3.3)	59 (3.9)	71 (4.7)	75 (4.9)
Maternal education								
<High school	619 (25.4)	302 (12.4)	97 (4.0)	71 (2.9)	84 (3.5)	87 (3.6)	22 (0.9)	34 (1.4)
High school	1,104 (33.8)	432 (13.2)	242 (7.4)	131 (4.0)	123 (3.8)	139 (4.3)	68 (2.1)	67 (2.1)
Some college	1,182 (37.5)	390 (12.4)	349 (11.1)	188 (6.0)	146 (4.6)	175 (5.6)	62 (2.0)	96 (3.0)
College+	1,143 (38.9)	265 (9.0)	363 (12.3)	189 (6.4)	111 (3.8)	138 (4.7)	59 (2.0)	78 (2.7)
Maternal BMI								
Underweight (<18.5)	229 (34.2)	90 (13.4)	60 (9.0)	29 (4.3)	19 (2.8)	27 (4.0)	9 (1.3)	10 (1.5)
Normal weight (18.5 <BMI <25)	2059 (35.0)	708 (12.0)	536 (9.1)	288 (4.9)	223 (3.8)	261 (4.4)	46 (0.8)	73 (1.2)
Overweight (25 <BMI <30	918 (36.0)	312 (12.2)	231 (9.0)	123 (4.8)	95 (3.7)	119 (4.7)	46 (1.8)	62 (2.4)
Obese (>30)	796 (35.3)	268 (11.9)	213 (9.5)	130 (5.8)	132 (5.9)	135 (6.0)	105 (4.7)	123 (5.5)
Missing information	94 (16.0)	34 (5.8)	15 (2.6)	13 (2.2)	2 (0.3)	4 (0.7)	6 (1.0)	9 (1.5)
Mother born in USA								
Yes	3,524 (38.0)	1,189 (12.8)	947 (10.2)	515 (5.6)	444 (4.8)	509 (5.5)	183 (2.0)	238 (2.6)
No	520 (20.6)	199 (7.9)	104 (4.1)	64 (2.5)	21 (0.8)	31 (1.2)	28 (1.1)	37 (1.5)

Characteristic	Any NSAID		Any decongestant		Any SABA/LABA		Any antihypertensive	
	Early pregnancy *N* = 4,096 (34.3%)	Late pregnancy *N* = 1,412 (11.8%)	Early pregnancy *N* = 1,055 (8.8%)	Late pregnancy *N* = 583 (4.9%)	Early pregnancy *N* = 471 (3.9%)	Late pregnancy *N* = 546 (4.6%)	Early pregnancy *N* = 212 (1.8%)	Late pregnancy *N* = 277 (2.3%)
Missing information	52 (35.1)	24 (16.2)	4 (2.7)	4 (2.7)	6 (4.1)	6 (4.1)	1 (0.7)	2 (1.4)
Language of interview								
English	3,873 (36.2)	1,322 (12.4)	1,018 (9.5)	554 (5.2)	465 (4.4)	539 (5.0)	202 (1.9)	264 (2.5)
Spanish	216 (18.2)	86 (7.3)	34 (2.9)	24 (2.0)	6 (0.5)	7 (0.6)	9 (0.8)	13 (1.1)
Interview translated	7 (9.3)	4 (5.3)	3 (4.0)	5 (6.7)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Parity								
Zero previous livebirths	1,978 (37.6)	580 (11.0)	481 (9.1)	257 (4.9)	206 (3.9)	239 (4.5)	91 (1.7)	123 (2.3)
1 previous livebirth	1,160 (32.7)	422 (11.9)	339 (9.5)	195 (5.5)	138 (3.9)	164 (4.6)	60 (1.7)	82 (2.3)
2 previous livebirths	583 (31.1)	245 (13.1)	170 (9.1)	87 (4.6)	87 (4.6)	94 (5.0)	38 (2.0)	42 (2.2)
3 previous livebirths	238 (30.4)	103 (13.1)	45 (5.7)	33 (4.2)	29 (3.7)	35 (4.5)	11 (1.4)	18 (2.3)
4+ previous livebirths	128 (28.4)	56 (12.4)	16 (3.5)	11 (2.4)	11 (2.4)	14(3.1)	11 (2.4)	11 (2.4)
Gravidity								
Primiparous	1,396 (36.6)	406 (10.7)	357 (9.4)	187 (4.9)	127 (3.3)	143 (3.8)	60 (1.6)	86 (2.3)
1 previous pregnancy	1,091 (32.8)	371 (11.2)	305 (9.2)	187 (5.6)	127 (3.8)	162 (4.9)	54 (1.6)	75 (2.3)
2 previous pregnancies	738 (33.6)	255 (11.6)	190 (8.7)	89 (4.1)	99 (4.5)	108 (4.9)	29 (1.3)	39 (1.8)
3 previous pregnancies	408 (31.9)	158 (12.4)	113(8.8)	60 (4.7)	50 (3.9)	63 (4.9)	36 (2.8)	43 (3.4)
4+ previous pregnancies	454 (34.6)	216 (16.4)	86 (6.5)	60 (4.6)	68 (5.2)	70 (5.3)	32 (2.4)	33 (2.5)
Previous stillbirth								
Yes	59 (31.2)	36 (19.0)	15 (7.9)	7 (3.7)	10 (5.3)	11 (5.8)	3 (1.6)	7 (3.7)
No	4,033 (34.3)	1,373 (11.7)	1,039 (8.8)	576 (4.9)	461 (3.9)	535 (4.6)	209 (1.8)	270 (2.3)
Previous abortion								
Yes	538 (39.4)	183 (13.4)	137 (10.0)	69 (5.1)	73 (5.3)	66 (4.8)	27 (2.0)	26 (1.9)
No	3,554 (33.6)	1,226 (11.6)	917 (8.7)	514 (4.9)	398 (3.8)	480 (4.5)	185 (1.7)	251 (2.4)
Previous miscarriage								
Yes	1,060 (36.6)	390 (13.4)	237 (8.2)	144 (5.0)	148 (5.1)	177 (6.1)	74 (2.6)	83 (2.9)
No	3,032 (33.5)	1,019 (11.3)	817 (9.0)	439 (4.9)	323 (3.6)	369 (4.1)	138 (1.5)	194 (2.1)
Previous tubal pregnancy								
Yes	63 (37.7)	26 (15.6)	16 (9.6)	3 (1.8)	10 (6.0)	15 (9.0)	4 (2.4)	5 (3.0)
No	4,029 (34.2)	1,383 (11.7)	1,038 (8.8)	580 (4.9)	461 (3.9)	531 (4.5)	208 (1.8)	272 (2.3)

Characteristic	Any NSAID		Any decongestant		Any SABA/LABA		Any antihypertensive	
	Early pregnancy *N* = 4,096 (34.3%)	Late pregnancy *N* = 1,412 (11.8%)	Early pregnancy *N* = 1,055 (8.8%)	Late pregnancy *N* = 583 (4.9%)	Early pregnancy *N* = 471 (3.9%)	Late pregnancy *N* = 546 (4.6%)	Early pregnancy *N* = 212 (1.8%)	Late pregnancy *N* = 277 (2.3%)
Previous molar pregnancy								
Yes	11 (22.9)	7 (14.6)	4 (8.3)	4 (8.3)	4 (8.3)	4 (8.3)	1 (2.1)	2 (4.2)
No	4,081 (34.3)	1,402 (11.8)	1,050 (8.8)	579 (4.9)	467 (3.9)	542 (4.6)	211 (1.8)	275 (2.3)
Planned pregnancy								
Yes	2,122 (32.3)	638 (9.7)	624 (9.5)	351 (5.3)	213 (3.2)	270 (4.1)	127 (1.9)	172 (2.6)
No	1,962 (36.8)	768 (14.4)	429 (8.1)	229 (4.3)	257 (4.8)	274 (5.1)	85 (1.6)	105 (2.0)
Prenatal care								
No prenatal care	47 (29.0)	32 (19.8)	12 (7.4)	5 (3.1)	3 (1.9)	3 (1.9)	0 (0.0)	2 (1.2)
By end of P3	3,416 (34.5)	1,082 (10.9)	914 (9.2)	497 (5.0)	413 (4.2)	467 (4.7)	183 (1.8)	237 (2.4)
P4 or later	512 (34.9)	246 (16.8)	105 (7.2)	64 (4.4)	43 (2.9)	57 (3.9)	21 (1.4)	30 (2.0)
Any fertility medication or procedure								
Yes	256 (39.8)	72 (11.2)	53 (8.2)	45 (7.0)	29 (4.5)	36 (5.6)	29 (4.5)	31 (4.8)
No	3,840 (34.0)	1,340 (11.9)	1,002 (8.9)	538 (4.8)	442 (3.9)	510 (4.5)	183 (1.6)	246 (2.2)
Multiple birth								
Singleton	3,856 (34.1)	1,347 (11.9)	1,016 (9.0)	555 (4.9)	441 (3.9)	507 (4.5)	194 (1.7)	250 (2.2)
Multiple	235 (38.2)	64 (10.4)	38 (6.2)	28 (4.6)	29 (4.7)	39 (6.3)	16 (2.6)	26 (4.2)
Year of due date								
1997–2001	1,008 (32.0)	413 (13.1)	393 (12.5)	201 (6.4)	118 (3.7)	170 (5.4)	41 (1.3)	56 (1.8)
2002–2006	1,454 (34.0)	504 (11.8)	440 (10.3)	245 (5.7)	197 (4.6)	204 (4.8)	71 (1.7)	87 (2.0)
2007–2011	1,634 (36.2)	495 (11.0)	222 (4.9)	137 (3.0)	156 (3.5)	172 (3.8)	100 (2.2)	134 (3.0)
Infant Sex								
Male	2,244 (34.4)	754 (11.6)	567 (8.7)	304 (4.7)	267 (4.1)	316 (4.8)	111 (1.7)	158 (2.4)
Female	1,847 (34.2)	658 (12.2)	485 (9.0)	279 (5.2)	203 (3.8)	229 (4.2)	99 (1.8)	118 (2.2)
Maternal smoking								
Any smoking between B1 and P3	1,148 (43.9)	467 (17.9)	273 (10.4)	138 (5.3)	159 (6.1)	174 (6.7)	42 (1.6)	50 (1.9)
No smoking between B1 and	2,916 (31.6)	929 (10.1)	779 (8.4)	441 (4.8)	307 (3.3)	368 (4.0)	169 (1.8)	225 (2.4)
Missing information	32 (30.5)	16 (15.2)	3 (2.9)	4 (3.8)	5 (4.8)	4 (3.8)	1 (1.0)	2 (1.9)
Maternal alcohol								

Characteristic	Any NSAID		Any decongestant		Any SABA/LABA		Any antihypertensive	
	Early pregnancy *N* = 4,096 (34.3%)	Late pregnancy *N* = 1,412 (11.8%)	Early pregnancy *N* = 1,055 (8.8%)	Late pregnancy *N* = 583 (4.9%)	Early pregnancy *N* = 471 (3.9%)	Late pregnancy *N* = 546 (4.6%)	Early pregnancy *N* = 212 (1.8%)	Late pregnancy *N* = 277 (2.3%)
Any drinking between B1 and P3	1,881 (43.9)	561 (13.1)	489 (11.4)	260 (6.1)	204 (4.8)	227 (5.3)	70 (1.6)	90 (2.1)
No drinking between B1 and P3	2,172 (28.8)	826 (11.0)	561 (7.4)	318 (4.2)	260 (3.5)	312 (4.1)	141 (1.9)	185 (2.5)
Missing information	43 (32.1)	25 (18.7)	5 (3.7)	5 (3.7)	7 (5.2)	7 (5.2)	1 (0.7)	2 (1.5)
Any injury in B1-P3								
Yes	158 (40.0)	53 (13.4)	53 (13.4)	18 (4.6)	22 (5.6)	21 (5.3)	8 (2.0)	8 (2.0)
None B3-EOP	3,675 (33.9)	1,252 (11.6)	925 (8.5)	527 (4.9)	400 (3.7)	472 (4.4)	195 (1.8)	262 (2.4)
Any injury in P4-EOP								
Yes	216 (35.9)	90 (15.0)	67 (11.1)	36 (6.0)	41 (6.8)	46 (7.7)	6 (1.0)	7 (1.2)
None B3-EOP	3,675 (33.9)	1,252 (11.6)	925 (8.5)	527 (4.9)	400 (3.7)	472 (4.4)	195 (1.8)	262 (2.4)
Diabetes								
Nondiabetic	3,679 (34.3)	1,253 (11.7)	968 (9.0)	529 (4.9)	424 (4.0)	490 (4.6)	146 (1.4)	209 (1.9)
Pre-existing diabetes (Type 1 or 2)	103 (38.4)	41 (15.3)	23 (8.6)	10 (3.7)	17 (6.3)	12 (4.5)	34 (12.7)	30 (11.2)
Pre-existing gestational diabetes	78 (33.3)	34 (14.5)	19 (8.1)	13 (5.6)	8 (3.4)	11 (4.7)	7 (3.0)	10 (4.3)
Type 1 or 2 diabetes during index pregnancy	4 (23.5)	2 (11.8)	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)	1 (5.9)	2 (11.8)
Gestational diabetes during index pregnancy	195 (34.4)	64 (11.3)	37 (6.5)	24 (4.2)	16 (2.8)	27 (4.8)	20 (3.5)	22 (3.9)
Ever told you had high blood pressure								
Yes	680 (38.9)	259 (14.8)	140 (8.0)	90 (5.1)	92 (5.3)	109 (6.2)	166 (9.5)	224 (12.8)
No	3,414 (33.5)	1,150 (11.3)	915 (9.0)	493 (4.8)	379 (3.7)	437 (4.3)	46 (0.5)	53 (0.5)
Pregnancy-related HBP								
Never diagnosed with HBP	3,414 (33.5)	1,150 (11.3)	915 (9.0)	493 (4.8)	379 (3.7)	437 (4.3)	46 (0.5)	53 (0.5)
HBP not related to this pregnancy	224 (38.5)	89 (15.3)	40 (6.9)	22 (3.8)	29 (5.0)	34 (5.8)	37 (6.4)	33 (5.7)
HBP in this pregnancy	439 (39.4)	161 (14.5)	92 (8.3)	63 (5.7)	60 (5.4)	72 (6.5)	125 (11.2)	187 (16.8)
Diagnosed after index pregnancy	17 (30.9)	9 (16.4)	8 (14.5)	5 (9.1)	3 (5.5)	3 (5.5)	4 (7.3)	4 (7.3)

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Characteristic	Any NSAID		Any decongestant		Any SABA/LABA		Any antihypertensive	
	Early pregnancy *N* = 4,096 (34.3%)	Late pregnancy *N* = 1,412 (11.8%)	Early pregnancy *N* = 1,055 (8.8%)	Late pregnancy *N* = 583 (4.9%)	Early pregnancy *N* = 471 (3.9%)	Late pregnancy *N* = 546 (4.6%)	Early pregnancy *N* = 212 (1.8%)	Late pregnancy *N* = 277 (2.3%)
Any kidney/bladder/UTI in B1-P3								
Yes	380 (34.1)	150 (13.5)	95 (8.5)	54 (4.8)	48 (4.3)	49 (4.4)	19 (1.7)	24 (2.2)
No	3,688 (34.3)	1,258 (11.7)	952 (8.8)	524 (4.9)	420 (3.9)	493 (4.6)	193 (1.8)	253 (2.4)
Any kidney/bladder/UTI in P4-EOP								
Yes	561 (33.9)	243 (14.7)	126 (7.6)	64 (3.9)	78 (4.7)	102 (6.2)	29 (1.8)	41 (2.5)
No	3,507 (34.3)	1,165 (11.4)	921 (9.0)	514 (5.0)	390 (3.8)	440 (4.3)	183 (1.8)	236 (2.3)
Have you ever had seizures?								
Yes	159 (37.3)	53 (12.4)	34 (8.0)	16 (3.8)	29 (6.8)	36 (8.5)	9 (2.1)	13 (3.1)
No	3,934 (34.2)	1,358 (11.8)	1,021 (8.9)	566 (4.9)	441 (3.8)	510 (4.4)	203 (1.8)	264 (2.3)
Site Id								
Arkansas	576 (38.4)	255 (17.0)	149 (9.9)	88 (5.9)	49 (3.3)	70 (4.7)	24 (1.6)	31 (2.1)
California	551 (27.7)	189 (9.5)	119 (6.0)	59 (3.0)	66 (3.3)	70 (3.5)	25 (1.3)	41 (2.1)
Iowa	449 (38.2)	161 (13.7)	141 (12.0)	71 (6.0)	60 (5.1)	67 (5.7)	27 (2.3)	34 (2.9)
Massachusetts	632 (43.4)	123 (8.4)	138 (9.5)	73 (5.0)	82 (5.6)	75 (5.1)	30 (2.1)	31 (2.1)
New York	278 (35.8)	105 (13.5)	63 (8.1)	33 (4.3)	52 (6.7)	54 (7.0)	13 (1.7)	19 (2.4)
Texas	351 (23.9)	179 (12.2)	121 (8.3)	68 (4.6)	28 (1.9)	47 (3.2)	21 (1.4)	28 (1.9)
CDC/Atlanta	440 (32.6)	161 (11.9)	149 (11.0)	92 (6.8)	40 (3.0)	66 (4.9)	25 (1.9)	33 (2.4)
North Carolina	391 (39.9)	128 (13.1)	88 (9.0)	43 (4.4)	48 (4.9)	50 (5.1)	32 (3.3)	34 (3.5)
Utah	428 (34.2)	111 (8.9)	87 (6.9)	56 (4.5)	46 (3.7)	47 (3.8)	15 (1.2)	26 (2.1)
Any reported exposure to known teratogen								
Yes	9 (50.0)	4 (22.2)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)
No	4,087 (34.3)	1,408 (11.8)	1,055 (8.8)	581 (4.9)	471 (3.9)	546 (4.6)	211 (1.8)	276 (2.3)

Note. “Early Pregnancy” = one month before conception through Day 139 of pregnancy; “Late Pregnancy” = Day 140 of pregnancy through end of pregnancy. Abbreviations: B1 = month before conception; BMI = body mass index; EOP = end of pregnancy; HBP = high blood pressure; LABA = long-acting beta agonist; NSAID = nonsteroidal anti-inflammatory drug; P3 = third month of pregnancy; P4 = fourth month of pregnancy; SABA = short-acting beta agonist; UTI = urinary tract infection.

TABLE 3

Risk estimates for stillbirth by early pregnancy vasoactive medication exposures, among case subjects, National Birth Defects Prevention Study 1997–2011

Early pregnancy exposures	Livebirth (*N* = 11,946)	Stillbirth (*N* = 448)	Crude OR (95% CI)
Any NSAID			
Unexposed	7,427 (64.6)	283 (66.6)	Ref
Exposed	4,096 (35.5)	143 (33.6)	0.9 (0.7,1.1)
Any decongestant			
Unexposed	10,402 (91.0)	400 (92.0)	Ref
Exposed	1,055 (9.2)	36 (8.3)	0.9 (0.6,1.3)
Any SABA/LABA			
Unexposed	11,261 (96.1)	428 (96.8)	Ref
Exposed	471 (4.0)	16 (3.6)	0.9 (0.5,1.5)
Any antihypertensive			
Unexposed	11,609 (98.2)	430 (96.8)	Ref
Exposed	212 (1.8)	14 (3.2)	1.8 (1.0,3.1)
Specific medications			
Any nonaspirin NSAID			
Unexposed	7,821 (67.8)	298 (69.8)	Ref
Exposed	3,732 (32.3)	130 (30.4)	0.9 (0.7,1.1)
Ibuprofen			
Unexposed	8,155 (70.5)	308 (72.1)	Ref
Exposed	3,434 (29.6)	120 (28.0)	0.9 (0.7,1.1)
Aspirin			
Unexposed	11,167 (94.2)	425 (95.7)	Ref
Exposed	698 (5.9)	19 (4.3)	0.7 (0.4,1.1)
Naproxen			
Unexposed	11,274 (94.8)	419 (93.9)	Ref
Exposed	616 (5.2)	27 (6.1)	1.2 (0.8,1.8)
Pseudoephedrine			
Unexposed	10,597 (92.2)	409 (93.4)	Ref

Early pregnancy exposures	Livebirth (*N* = 11,946)	Stillbirth (*N* = 448)	Crude OR (95% CI)
Exposed	919 (8.0)	30 (6.8)	0.8 (0.6,1.2)
Albuterol			
Unexposed	11,420 (96.4)	431 (97.1)	Ref
Exposed	429 (3.6)	15 (3.4)	0.9 (0.5,1.6)

Note. "Early pregnancy"= one month before conception through Day 139 of pregnancy. Unexposed reference group for all exposure groups = no exposure from one month before conception through the end of pregnancy.

TABLE 4

Risk estimates for stillbirth by late pregnancy vasoactive medication exposures, among case subjects, National Birth Defects Prevention Study 1997–2011

Late pregnancy exposures	Livebirth (*N* = 11,946)	Stillbirth (*N* = 448)	Crude HR (95% CI)
Any NSAID			
Unexposed	7,427 (83.9)	283 (82.5)	Ref
Exposed	1,412 (16.0)	60 (17.5)	0.9 (0.6,1.3)
Any decongestant			
Unexposed	10,402 (94.6)	400 (97.8)	Ref
Exposed	583 (5.3)	9 (2.2)	0.6(0.2,1.9)
Any SABA/LABA			
Unexposed	11,261 (95.4)	428 (96.2)	Ref
Exposed	546 (4.6)	17 (3.8)	0.7(0.3,1.3)
Any antihypertensive			
Unexposed	11,609 (97.7)	430 (96.6)	Ref
Exposed	277 (2.3)	15 (3.4)	2.0(1.1,3.6)
Specific medications			
Any nonaspirin NSAID			
Unexposed	7,821 (86.3)	298 (84.9)	Ref
Exposed	1,231 (13.6)	53 (15.1)	0.9 (0.6,1.3)
Ibuprofen			
Unexposed	8,155 (87.9)	308 (86.3)	Ref
Exposed	1,116 (12.0)	49 (13.7)	1.0 (0.7,1.4)
Aspirin			
Unexposed	11,167 (97.6)	425 (97.5)	Ref
Exposed	268 (2.3)	11 (2.5)	0.7 (0.3,1.6)
Naproxen			
Unexposed	11,274 (98.5)	419 (98.1)	Ref
Exposed	171 (1.5)	8 (1.9)	0.8(0.3,2.2)
Pseudoephedrine			
Unexposed	10,597 (95.3)	409 (98.1)	Ref
Exposed	516 (4.6)	8 (1.9)	0.7 (0.2,2.2)

Late pregnancy exposures	Livebirth (*N* = 11,946)	Stillbirth (*N* = 448)	Crude HR (95% CI)
Albuterol			
Unexposed	11,420 (96.6)	431 (96.9)	Ref
Exposed	398 (3.4)	14 (3.1)	0.6(0.3,1.3)

Note. "Late pregnancy"= Day 140 of pregnancy through end of pregnancy.