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Maternal Vasoactive Exposures, Amniotic Bands, and Terminal Transverse Limb Defects

Martha M. Werler¹, Jaclyn L. F. Bosco¹, Stuart K. Shapira², and National Birth Defects Prevention Study

¹ Slone Epidemiology Center at Boston University, Boston, MA

² National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

Abstract

BACKGROUND—Limb reduction deficiencies that are accompanied by amniotic bands (AB-L) and terminal transverse limb deficiencies (TLD) have each been attributed to vascular disruption; for the former, however, it is not clear if amniotic bands are the primary cause of or are secondary to vascular disruption. If amniotic bands are secondary to vascular disruption, then a shared pathogenesis for each case group might be exhibited by similar risk factors.

METHODS—We evaluated maternal age, education, race/ethnicity, parity, pregnancy wantedness, and vasoactive exposures among 139 AB-L and 373 TLD cases, using interview data collected from mothers in ten states by the National Birth Defects Prevention Study. Vasoactive exposures included maternal cigarette smoking and use of decongestants, non-steroid anti-inflammatory drugs, and anti-hypertensive drugs in the periconceptional period.

RESULTS—Increased risk estimates were observed for Black mothers (odds ratio=2.5, 95% confidence interval=1.5–4.1) and nulliparous mothers (2.1, 1.4–3.0) in relation to AB-L, while neither was associated with TLD. Hispanic women (1.4, 1.0–1.9) and those not wanting the pregnancy (1.5, 1.1–2.1) had increased risks of TLD, but not AB-L. Maternal cigarette smoking and aspirin use each increased the risk of AB-L, but not TLD; while decongestants and possibly antihypertensive medications increased the risk of TLD, but not AB-L.

CONCLUSIONS—The lack of consistent findings for the two case groups suggests that AB-L and TLD may be distinct entities. The inconsistencies also suggest that these vasoactive exposures may not be markers for vascular disruption or that vascular disruption may not play a major role in the pathogenesis of these two types of limb deficiencies.

A variety of congenital anomalies are thought to result, at least in some instances, from a vascular disruptive process during gestation, including gastroschisis, small intestinal atresia, terminal transverse limb reduction defects, renal agenesis, microtia, and clubfoot (Van Allen, 1981). Defects that are accompanied by the presence of so-called ‘amniotic bands’ – presumably fibrous tissue that originated in the amniotic lining – have also been attributed to vascular disruption, but whether the vascular disruption is primary or secondary relative to fibrous bands is not clear (McGuirk and others, 2001; Moerman and others, 1992). The proposed pathogenesis for primary vascular disruption of amniotic bands is that occlusion of a developing limb causes necrosis at the terminus, which adheres to and pulls off strips of

Corresponding author: Martha M. Werler, Sc.D., Slone Epidemiology Center at Boston University, 1010 Commonwealth Ave., Boston, MA 02215, T: 617-734-6006, mwerler@slone.bu.edu.

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amnion, resulting in mechanical damage to the fetus, such as constriction bands and clefts. The necrotic tissue eventually heals, and the presence at birth of fibrous bands prompts the diagnosis of amniotic band sequence. If this pathogenesis does indeed exist for amniotic bands, then terminal transverse limb reductions (TLD) without evidence of amniotic bands could be considered another form of the same underlying defect.

In this study, we aimed to compare epidemiologic characteristics between limb defects with and without evidence of amniotic bands and to determine whether maternal exposures in the two groups support the vascular disruption hypothesis, using data from the National Birth Defects Prevention Study. First, we evaluated whether the patterns of demographic and reproductive factors are similar or different for the two case groups. Second, we estimated relative risks associated with maternal cigarette smoking and use of vasoactive medications because they have previously been associated with other vascular disruption defects, such as gastroschisis, small intestinal atresia, hemifacial microsomia, and clubfoot (Honein and others, 2000; Werler and others, 1992; Werler and others, 2002).

Methods

The National Birth Defects Prevention Study (NBDPS) is a population-based case-control study of birth defects that began in 1998 and continues today. Birth defect registries in ten states (Arkansas, California, Iowa, Georgia, Massachusetts, New Jersey (1998–2002), New York, North Carolina (2003–), Texas, and Utah (2003–)) report cases with selected structural defects and non-malformed controls to the NBDPS. Mothers of cases and controls are invited to participate within 24 months after the expected due date in a telephone interview, which asks questions about demographic reproductive factors, behaviors, illnesses and medication use. The institutional review boards in each state approved the study protocol.

For this analysis, study subjects are mothers whose pregnancy due dates were between October 1, 1997 and December 31, 2004. Records for cases diagnosed with amniotic bands or limb deficiency, were reviewed and classified. To be included as a case of amniotic bands, there had to be constriction rings, fibrous strands, or atypical syndactylies, such as acrosyndactyly. Cases with evidence of amniotic bands or constriction rings, but no limb involvement or with evidence of body wall complex were not considered for this analysis. Cases with evidence of amniotic bands or constriction rings and limb involvement (AB-L) were further categorized as ‘isolated AB-L’ if only limbs had amniotic band constrictions or amputations (i.e., no craniofacial or truncal involvement). Cases diagnosed with a limb amputation, absence, or hypoplasia of distal limb structure, but without amniotic bands, were classified as terminal transverse reductions (TLDs). Cases of wrist, mid-arm, or upper arm amputations with nubbins present were included. Cases of longitudinal or intercalary limb deficiency were excluded, as were cases of digit hypoplasia without radiographic evidence of limb reduction. Cases with TLD were further categorized as ‘isolated TLD’ if only limb defects were present (i.e., no other major malformations).

Mothers were asked standardized questions about their age, years of education, race/ethnicity, number of previous births, whether the pregnancy was wanted or not, and the number of cigarettes smoked per day before and during pregnancy. For maternal race, mothers with Hispanic ethnicity were considered as such, regardless of race. Questions were asked about medications taken for specific illnesses (e.g., cold or flu, hypertension, asthma) and about specifically named products (e.g., Tylenol, Advil, Aspirin, Aleve). For cigarette smoking and medication use, exposures were tabulated for the periconceptional period, encompassing the period beginning two weeks before the last menstrual period and ending 14 weeks after the last menstrual period. Women who changed their smoking amount were assigned the largest reported number of cigarettes smoked per day during this period. Components of reported

medications were categorized according to their purported vasoactivity: 1) vasoconstrictors, comprising mostly decongestants and bronchial dilators; 2) non-steroidal anti-inflammatory drugs (NSAIDs), comprising non-aspirin NSAIDs and aspirin; and 3) vasodilators, comprising antihypertensive medications.

Frequency distributions of maternal factors, cigarette smoking, and vasoactive medications were tabulated for cases and controls. Odds ratios were estimated when there were at least five exposed cases from logistic regression models, controlling for age, education, parity, race/ethnicity, cigarette smoking, medication use, and state of maternal residence. Computations and estimations were conducted with SAS version 9.1 (Cary, NC).

Results

Of 185 study subjects identified with amniotic bands, 139 were classified as AB-L and of these, 119 were isolated AB-L. Of 656 study subjects identified with limb deficiencies, 373 were classified as TLD and of these, 318 were isolated TLD. The distributions of maternal age, years of education, race/ethnicity, and parity are shown in Table 1 for case and control mothers. Mothers of AB-L cases were younger and less educated than mothers of TLD and control mothers. AB-L, TLD, and control mothers had different race/ethnicity distributions, with 21% of AB-L case mothers identifying themselves as Black, compared to 8% of TLD mothers and 11% of control mothers. Almost 30% of TLD mothers identified as Hispanic, compared to 19% of AB-L mothers and 22% of control mothers. While 45% of TLD cases and 40% of controls were first births, approximately 60% of AB-L cases were first births. There was little difference in the distributions of pregnancy wantedness across the case and control groups.

Multivariate-adjusted odds ratios for the younger, least educated, and non-White groups of mothers; first births; and unwanted pregnancies are shown in Table 2. Risk estimates for AB-L mothers who were <25 years old, had <12 years of education, were Black, or who had a first birth were 1.5 (95% confidence interval, 1.0 to 2.1), 1.2 (0.8 to 2.0), 2.5 (1.5 to 4.1), and 2.1 (1.4 to 3.0), respectively. Risk estimates for AB-L in relation to Hispanic ethnicity, Asian race, and not wanting to be pregnant were close to the null. For TLD, the pattern of adjusted odds ratios was generally opposite that for AB-L. Hispanic mothers and mothers not wanting to be pregnant had slightly increased risks of TLD; adjusted odds ratios were 1.4 (1.0 to 1.9) and 1.5 (1.1 to 2.1), respectively. No increases in risk were estimated for age <25 years, education <12 years, Black or Asian race, and first birth. Odds ratios for each of the isolated case subgroups were similar to the respective overall groups.

The distributions and odds ratio estimates for periconceptional vasoactive exposures are shown in Tables 3 and 4, respectively. Cigarette smoking was more common in mothers of AB-L cases than in mothers of TLD cases or controls. Compared to controls, the AB-L odds ratio for ≤ 14 cigarettes per day was increased 1.4-fold (0.9 to 2.3) and for ≥ 15 cigarettes per day it was increased 2.4-fold (1.3 to 4.4). There was no apparent association between smoking and risk of TLD. For medication use, AB-L mothers reported rates of vasoconstrictor use (10.8%) that were similar to those of control mothers (12.9%), but higher rates of NSAID use (36.0% versus 25.9%). Adjusted odds ratios were increased 1.5-fold (1.0 to 2.2) for non-aspirin NSAIDs and 2.1-fold for aspirin (1.2 to 3.9). Odds ratios for isolated AB-L were similar to those estimated for AB-L overall. No mothers of AB-L cases reported use of vasodilator medication. Contrary to AB-L, more TLD mothers reported vasoconstrictor use (16.4%), particularly decongestant use (13.9%), than control mothers (12.9% and 10.4%). The adjusted odds ratio for decongestant use in relation to TLD was 1.5 (1.1 to 2.1), and in relation to isolated TLD it was 1.7 (1.2 to 2.3). For NSAIDs overall, non-aspirin NSAIDs, and aspirin, slightly increased odds ratios were observed in relation to TLD, although the null was not excluded in each 95% confidence interval. The mothers of seven (1.9%) TLD cases reported use of vasodilator medications, five

(1.6%) of whom were isolated TLD, compared to 1.1% of controls. Adjusted odds ratios were 1.8 (0.8 to 4.0) and 1.5 (0.6 to 3.8) for TLD and isolated TLD, respectively.

Discussion

We hypothesized that similar epidemiologic characteristics for AB-L and TLDs would suggest that these case groups share a common pathogenesis, possibly vascular disruption as the primary event, with the presence of fibrous bands or constriction rings in AB-L cases being a secondary occurrence. Our findings contradict this hypothesis, suggesting that AB-L may be a different entity than TLD. Demographic, reproductive and vasoactive factors found to increase the risk of one appeared to have no effect on the other phenotype. Black, nulliparous, and possibly young mothers each had increased risks of overall and isolated AB-L, but not TLD, while Hispanic mothers had a slight increase in risk of TLD (with borderline significance) but not AB-L. First births were more than twice as likely in the AB-L group, while unwanted pregnancies were 50% more likely in the TLD group. Similarly, odds ratios for maternal cigarette smoking and vasoactive medication use were inconsistent across the two case groups.

Despite differing demographic and reproductive characteristics for AB-L and TLD, vascular disruption might still play a role in the development of each phenotype, as is purported for a range of defects with differing epidemiologic features, such as gastroschisis, small intestinal atresia, and renal agenesis (Van Allen, 1981). We examined maternal exposure to vasoactive agents as indicators of vascular disruption, and found evidence both in support and against this hypothesized pathogenesis. In support, we observed that 1) mothers who smoked ≥ 15 cigarettes per day had increased risks of AB-L, 2) slightly elevated (but not statistically significant) odds ratios were observed for periconceptional use of non-aspirin NSAIDs in relation to both case groups, and 3) periconceptional decongestant use and possibly vasodilator use increased the risks of TLDs. Conversely, vasoconstrictor use was reported by fewer AB-L case mothers and cigarette smoking was not associated with TLD. It is not possible to reconcile the varying effects of these agents on the two case groups without understanding more precisely their respective pathogenic processes and the pharmacology in the fetus of components of cigarettes, alpha- and beta-adrenergic stimulants, inhibitors of the different COX pathways, and the range of antihypertensive drugs. Unfortunately, at present, little is known about these aspects of embryologic and fetal development. These findings do suggest that pathogenesis and etiologic factors for AB-L and TLD may indeed differ. Timing of exposures is undoubtedly important in relation to risk of each of these defects, as the sensitivity will be greater or less during different developmental periods. Further, these case groups may well result from several different etiologies and pathogeneses, and those processes may overlap across these phenotypes. For example, maternal cigarette smoking may cause vascular disruption that produces both TLDs and amniotic bands, but a relatively larger proportion of the latter might be attributed to smoking due to etiologic heterogeneity within each case group. It is also possible that each defect is sensitive at different doses; perhaps the levels of exposure to cigarette smoke and vasoactive medications in this study are too low to observe a strong vascular disruptive effect for both defect groups. The inconsistent findings across case groups and exposures also suggest that these vasoactive exposures may not be markers for vascular disruption or that vascular disruption may not play a major role in the pathogenesis of these two types of limb deficiencies.

Young age (Bower and others, 1993; Garza and others, 1988; Werler and others, 2003), lower levels of education (Czeizel and others, 1994; Werler and others, 2003), Black race (Garza and others, 1988; Werler and others, 2003), and first births (Bower and others, 1993; Garza and others, 1988) have each been linked to amniotic bands, consistent with our observations. The increased risks for first birth and possibly for young maternal age reported here and in the earlier study by Werler (2003) are independent of the effects of each other, as well as the effects

of educational level, race/ethnicity, and planned pregnancy. Nevertheless, their associations might be confounded by exposures that are most prevalent in young women or first pregnancies. On the other hand, young maternal age and first birth may represent immature reproductive physiology or some other biologic factors. One study found that mothers of AB-L cases were more likely to report not wanting the pregnancy (Czeizel and others, 1993), contrary to the null association observed in our study. Most studies of limb reduction defects do not examine sub-types such as TLDs, which hampers valid comparisons with our findings. Contrary to our observations, Lin (Lin and others, 1993) showed more TLDs born to young mothers in comparison to other LRDs.

Our positive association of maternal smoking in pregnancy in relation to AB-L is consistent with two studies (Czeizel and others, 1993; Wasserman and others, 1996), but in contrast to a null finding in another study (Werler and others, 2003). For TLD, our null finding for heavy smoking is consistent with Czeizel (1994), but both Wasserman (1996) and Kallen (1997) observed increases in risk. Thus, our findings for cigarette smoking are consistent with some and inconsistent with others, suggesting further investigations of smoking and amniotic bands or limb reduction sub-types are necessary before conclusions can be made. Cigarette smoking has been associated with increased risks of various other vascular disruption defects (Haddow and others, 1993; Torfs and others, 1994), hemifacial microsomia (Werler and others, 2004), renal agenesis (Kallen, 1997; Li and others, 1996) and clubfoot (Alderman and others, 1991; Honein and others, 2000; Skelly and others, 2002). These positive associations are considered as evidence in favor of vascular disruption, just as we have discussed for our observed associations with AB-L. However, the products of cigarette smoke include thousands of potentially toxic compounds, and the possibility that increased risks represent another pathogenesis cannot be excluded. Animal models of vascular disruption show that hypoxia plays a role when the disruption involves occlusion (Webster and Abela, 2007). The carbon monoxide contained in cigarette smoke has been linked to fetal hypoxia (Werler, 2006), suggesting this pathogenic mechanism should also be considered.

Evidence in favor of vascular disruption as the primary cause of amniotic bands rests partially on experimental evidence of amniotic band-like limb defects, including amputations, distal reductions, and distal necrosis (Kino, 1975; Webster and Brown-Woodman, 1990), and partially on the presence of internal malformations that cannot result from mechanical damage from amniotic bands in cases with clear external amniotic band disruptions (Hunter and Carpenter, 1986). The strongest support for vascular disruption as a cause of limb reductions comes from the animal literature, where vessel constriction (Brent and Franklin, 1960; Webster and others, 1987), amniocentesis (Kino, 1975), and high dose cocaine exposures (Webster and Brown-Woodman, 1990) have induced amniotic band-like limb reduction phenotypes, but without fibrous bands. These animal experiments, although intriguing, represent extreme circumstances relative to human gestation. Clinical observations offer further support on a case-by-case basis. Cases of monozygous twinning, tubal pregnancies, bicornate uterus, misoprostol, or chorionic villous sampling associated with the amniotic band phenotype (McGuirk and others, 2001; Stoler and others, 1999; Van Allen, 1981) offer compelling evidence for a vascular disruption etiology, but these published cases appear to represent a very small fraction of most amniotic band or limb reduction cases.

Decongestant, bronchodilator, non-aspirin NSAID, and aspirin exposures previously have not been studied in relation to amniotic band defects or limb reduction defects in humans. Antihypertensive medications, as a group, have also not been studied in relation to these defects, but calcium channel blockers were reported not to be associated with limb deficiencies overall in a study with only two exposed cases (Sorensen and others, 2001). Decongestant (Torfs and others, 1996; Werler and others, 1992; Werler and others, 2002), NSAID (Torfs and others, 1996; Werler and others, 2004), and aspirin use (Drongowski and others, 1991;

Martinez-Frias and others, 1997; Torfs and others, 1996; Werler and others, 1992; Werler and others, 2002) have been associated with other vascular disruption-type defects, but only animal data link vasoconstrictor exposures to limb defects (Gilbert-Barness and Drut, 2000; Werler, 2006). In addition, high doses of calcium channel blockers in animals induce limb defects similar to those observed from vascular occlusion studies (Danielsson and others, 1989).

Although this is the largest epidemiologic study of amniotic bands to date, our findings on vasoconstrictive and vasodilator medications are limited by small numbers. Information was collected on timing, frequency, and dose of medications (to the extent possible), but small numbers prevented such detailed analyses. Also, the demographic and reproductive factors that we examined in this study are related to one another, making estimation of independent effects less precise, despite reasonable numbers of observations for most factors. In addition, retrospective data collection, sometimes as much as 34 months after the onset of pregnancy, may hamper accurate reporting of exposures, particularly those that are episodic like decongestants and analgesics. Recall bias, where the accuracy of reporting by case mothers is different than that by control mothers, is an unlikely explanation for our observations. Increased, decreased, and null odds ratios were observed across the different medication and case group comparisons, suggesting case mothers do not tend to report more or less accurately than controls. However, poor recall overall is possible, in which case odds ratio estimates may be shifted toward the null. Residual confounding is also possible, including confounding by the indications such as fever or the infection for which the different vasoactive medications were taken. Finally, misclassification of the case types is possible. Classifications relied on documentation in medical records; if amniotic band tissue, a constriction band, or digit syndactylies typical of amniotic banding were not mentioned in the records of a case with a limb reduction, they were presumed absent, and the case would have been classified in the TLD category, even if the underlying etiology was actually amniotic bands. However, large amounts of such misclassification would be necessary to explain some of the different findings between the two case groups, such as those observed for maternal age, first birth, and cigarette smoking.

In conclusion, the patterns of demographic, reproductive, and vasoactive risk factors across limb-affected amniotic bands and terminal limb reduction defects suggest that these phenotypes are different entities. These findings offer some clues to the debate about etiologies and pathogeneses of amniotic bands and limb defects, but epidemiologic data will be more informative once clinical and experimental pharmacology and embryology studies better characterize fetal exposures and development.

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Frequency distributions of demographic and reproductive factors among mothers of AB-L and TLD cases and controls, National Birth Defects Prevention Study.

Table 1

Maternal Factor	AB-L (N=139)		Isolated AB-L (N=119)		TLD (N=373)		Isolated TLD (N=318)		Control (N=5958)	
	N	%	N	%	N	%	N	%	N	%
Age:										
<20 yr old	27	19.4	21	17.6	45	12.1	40	12.6	658	11.0
20-24 yr old	45	32.4	40	33.6	89	23.9	71	22.3	1350	22.7
25-29 yr old	31	22.3	25	21.0	91	24.4	81	25.5	1568	26.3
30+	36	25.9	33	27.7	148	39.7	126	39.6	2382	40.0
Education:										
<12 years	31	22.3	25	21.0	61	16.4	51	16.0	991	16.6
12 yr education	40	28.8	32	26.9	98	26.3	80	25.2	1471	24.7
13-15 yr education	33	23.7	30	25.2	106	28.4	92	28.9	1564	26.3
16+ yr education	31	22.3	28	23.5	101	27.1	90	28.3	1843	30.9
Missing education	4	2.9	4	3.4	7	1.9	5	1.6	89	1.5
Race/ethnicity:										
White	48	34.5	46	38.7	185	49.6	162	50.9	3184	53.4
Black	29	20.9	25	21.0	31	8.3	23	7.2	679	11.4
Hispanic	26	18.7	20	16.8	110	29.5	93	29.3	1328	22.3
Asian	8	5.8	5	4.2	8	2.1	8	2.5	176	3.0
Other/unknown	28	20.2	23	19.4	39	10.4	32	10.1	591	10.0
Parity:										
First birth	85	61.2	71	59.7	166	44.5	142	44.7	2381	40.0
Pregnancy wantedness:										
Wanted to be pregnant then	60	43.2	53	44.5	164	44.0	143	45.0	2843	47.7
Wanted to wait until later	25	18.0	20	16.8	60	16.1	47	14.8	910	15.3
Did not want pregnancy	14	10.1	13	10.9	52	13.9	42	13.2	594	10.0
Did not care	13	9.4	11	9.2	36	9.7	30	9.4	465	7.8
Refused/unknown	1	0.7	0	-	1	0.3	0	-	12	0.2

Maternal Factor	AB-L (N=139)		Isolated AB-L (N=119)		TLD (N=373)		Isolated TLD (N=318)		Control (N=5958)	
	N	%	N	%	N	%	N	%	N	%
Missing*	26	18.7	22	18.5	60	16.1	56	17.6	1134	19.0

* Data were not collected.

Table 2
Adjusted odds ratios (and 95% confidence intervals) for demographic and reproductive factors in relation to risk of AB-L and TLD in offspring, National Birth Defects Prevention Study.

Maternal Factor	AB-L (N=139)		Isolated AB-L (N=119)		TLD (N=373)		Isolated TLD (N=318)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age:								
<25 yr old	1.5	(1.0, 2.1)	1.5	(1.0, 2.2)	1.0	(0.8, 1.3)	1.1	(0.8, 1.4)
Education:								
<12 years	1.2	(0.8, 2.0)	1.2	(0.7, 2.0)	0.8	(0.6, 1.1)	0.8	(0.6, 1.1)
Race/ethnicity:								
Black	2.5	(1.5, 4.1)	2.4	(1.4, 4.0)	0.8	(0.5, 1.1)	0.6	(0.4, 1.0)
Hispanic	0.8	(0.5, 1.5)	0.8	(0.4, 1.4)	1.4	(1.0, 1.9)	1.3	(1.0, 1.8)
Asian	1.0	(0.4, 2.9)	0.8	(0.2, 2.4)	0.5	(0.2, 1.3)	0.7	(0.3, 1.8)
Parity:								
First birth	2.1	(1.4, 3.0)	2.0	(1.3, 2.9)	1.2	(1.0, 1.5)	1.2	(1.0, 1.5)
Pregnancy wantedness:								
Did not want	0.8	(0.4, 1.4)	0.9	(0.5, 1.6)	1.5	(1.1, 2.1)	1.5	(1.0, 2.1)

Table 3
Vasoactive exposures among mothers of AB-L and TLD cases and controls, National Birth Defects Prevention Study.

Periconceptional Exposure	AB-L (N=139)		Isolated AB-L (N=119)		TLD (N=373)		Isolated TLD (N=318)		Control (N=5958)	
	N	%	N	%	N	%	N	%	N	%
Cigarette smoking:										
≤14 cig/day	25	18.0	23	19.3	51	13.6	42	13.2	784	13.2
15+ cig/day	15	10.8	11	9.2	22	5.9	21	6.6	338	5.7
Unknown	4	2.9	4	3.4	6	1.6	4	1.3	72	1.2
Medication *										
Vasoconstrictors	15	10.8	14	11.8	61	16.4	52	16.4	767	12.9
Decongestants	9	6.5	8	6.7	52	13.9	47	14.8	617	10.4
Bronchodilators	5	3.6	5	4.2	12	3.2	8	2.5	177	3.0
NSAIDs	50	36.0	42	35.3	110	29.5	96	30.2	1545	25.9
Non-aspirin NSAIDs	43	30.9	35	29.4	99	26.5	86	27.0	1387	23.3
Aspirin	13	9.4	13	10.9	20	5.4	18	5.7	265	4.5
Vasodilators	0	-	0	-	7	1.9	5	1.6	64	1.1

* Timing was reported as unknown or missing for 114 vasoconstrictor, 114 NSAID, and 42 vasodilator exposed women.

Table 4

Adjusted ORs (and 95% confidence intervals) for maternal vasoactive exposures in relation to risk of AB-L and TLD in offspring, National Birth Defects Prevention Study.

Periconception Exposure	AB-L (N=139)		Isolated AB-L (N=119)		TLD (N=373)		Isolated TLD (N=318)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cigarette smoking:								
≤14 cig/day	1.4	(0.9, 2.3)	1.5	(0.9, 2.4)	1.1	(0.8, 1.5)	1.0	(0.7, 1.5)
15+ cig/day	2.4	(1.3, 4.4)	1.9	(1.0, 3.8)	1.1	(0.7, 1.7)	1.2	(0.8, 1.9)
Medication * :								
Vasoconstrictors								
Decongestants	0.9	(0.5, 1.5)	0.9	(0.5, 1.7)	1.4	(1.1, 1.9)	1.4	(1.1, 2.0)
Bronchodilators	0.7	(0.3, 1.3)	0.7	(0.3, 1.4)	1.5	(1.1, 2.1)	1.7	(1.2, 2.3)
NSAIDs	1.2	(0.5, 3.0)	1.3	(0.5, 3.4)	1.1	(0.6, 2.0)	0.9	(0.4, 1.8)
Non-aspirin NSAIDs	1.6	(1.1, 2.3)	1.5	(1.0, 2.2)	1.3	(1.0, 1.6)	1.3	(1.0, 1.7)
Aspirin	1.5	(1.0, 2.2)	1.4	(0.9, 2.1)	1.3	(1.0, 1.6)	1.3	(1.0, 1.7)
Vasodilators	2.1	(1.2, 3.9)	2.5	(1.4, 4.6)	1.2	(0.8, 2.0)	1.3	(0.8, 2.2)
	-	-	-	-	1.8	(0.8, 4.0)	1.5	(0.6, 3.8)

* Women whose timing of use was reported as unknown or missing were excluded.