

Appendix 1. Acknowledgments

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Appendix 2. Reported Prescription Antiemetic Medications (other than Ondansetron) and Frequency of Use among Controls, NBDPS and BDS

	Frequency of Use n (%)	
	NBDPS (1997-2011)	BDS (1997-2014)
Total Controls	6751	5873
Prescription Antiemetic		
Hydroxyzine	6 (0.09)	2 (0.03)
Promethazine	320 (4.7)	63 (1.1)
Trimethobenzamide	2 (0.03)	3 (0.05)
Chlorpromazine	1 (0.01)	0
Prochlorperazine	20 (0.3)	15 (0.3)
Cisapride	0	0
Metoclopramide	45 (0.7)	36 (0.6)
Parenteral fluids	40 (0.6)	35 (0.6)

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Appendix 3. Crude Odds Ratios and 95% Confidence Intervals for Ondansetron and All Defects, National Birth Defects Prevention Study (NBDPS) and Birth Defect Study (BDS)

	NBDPS (2005-2011)			BDS (1997-2014)		
	Total	No. Exposed	OR(95% CI)	Total	No. Exposed	OR(95% CI)
Controls	6751	253		5873	375	
Neural Tube Defects						
<i>Anencephaly and craniorachischisis</i>	101	6	0.9 (0.4, 2.0)	7	---	---
<i>Spina bifida</i>	311	18	0.9 (0.5, 1.5)	150	15	1.6 (0.9, 2.8)
Oral Clefts						
<i>Cleft palate only</i>	418	40	1.5 (1.1, 2.2)	287	11	0.6 (0.3, 1.1)
<i>Cleft lip w/wo cleft palate</i>	828	56	1.0 (0.8, 1.4)	477	27	0.9 (0.6, 1.3)
Hypospadias[†]						
<i>first/second/third degree</i>	n/c	---	---	402	30	1.4 (0.9, 2.1)
<i>second/third degree</i>	713	45	1.1 (0.7, 1.5)	94	---	---
NBDPS (1997-2011)						
Septal defects						
<i>VSD[‡]</i>	1345	27	0.5 (0.4, 0.8)	1327	114	1.4 (1.1, 1.7)
<i>ASD secundum</i>	1205	41	0.9 (0.7, 1.3)	364	24	1.0 (0.7, 1.6)
Renal collecting system defects	n/c	---	---	817	74	1.5 (1.1, 1.9)
NON-CARDIAC						
Amniotic band	155	5	0.9 (0.3, 2.1)	51	---	---
Brain						
Absent corpus collosum	n/c	---	---	110	8	1.2 (0.6, 2.4)
Hydrocephaly	254	11	1.2 (0.6, 2.1)	43	---	---
Ear						
Anotia/microtia	354	10	0.7 (0.4, 1.4)	41	---	---
Eye						
Anophthalmia/ microphthalmia	132	4	0.8 (0.3, 2.2)	21	---	---
Cataract	207	8	0.9 (0.4, 1.8)	35	---	---
Gastrointestinal						
Anorectal atresia/stenosis	556	15	0.7 (0.4, 1.2)	114	5	0.7 (0.3, 1.7)
Biliary atresia	101	5	1.3 (0.5, 3.2)	9	---	---
Esophageal atresia	363	10	0.7 (0.4, 1.4)	73	---	---

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Hirschsprung	n/c	---	---	110	10	1.4 (0.7, 2.8)
Intestinal malrotation	n/c	---	---	125	10	1.3 (0.7, 2.5)
Pyloric stenosis	n/c	---	---	370	20	0.9 (0.5, 1.4)
Small intestinal atresia/stenosis	238	7	0.8 (0.4, 1.7)	155	12	1.2 (0.7, 2.2)
Musculoskeletal						
Clubfoot	n/c	---	---	404	29	1.1 (0.8, 1.7)
Craniosynostosis	908	54	1.7 (1.2, 2.2)	66	---	---
Diaphragmatic hernia	458	23	1.4 (0.9, 2.1)	89	---	---
Gastroschisis	763	17	0.6 (0.4, 1.0)	194	16	1.3 (0.8, 2.3)
Limb deficiency	601	16	0.7 (0.4, 1.2)	129	7	0.9 (0.4, 1.9)
<i>Longitudinal</i>	217	5	0.6 (0.2, 1.5)	35	---	---
<i>Longitudinal Preaxial</i>	125	4	0.8 (0.3, 2.3)	17	---	---
<i>Transverse</i>	363	9	0.7 (0.3, 1.3)	70	---	---
Omphalocele	187	6	0.9 (0.4, 2.0)	52	---	---
Genitourinary						
Cystic kidney	n/c	---	---	176	19	1.8 (1.1, 2.9)
Extra/horseshoe kidney	n/c	---	---	129	10	1.2 (0.6, 2.4)
Renal agenesis/dysgenesis	74	---	---	159	22	2.3 (1.5, 3.7)
Undescended testicle †	n/c	---	---	538	44	1.5 (1.1, 2.1)
CARDIAC						
Heterotaxy	185	4	0.6 (0.2, 1.5)	26	---	---
Single ventricle	155	7	1.2 (0.6, 2.6)	22	---	---
Conotruncal Anomalies	1382	45	0.9 (0.6, 1.2)	502	30	0.9 (0.6, 1.4)
<i>Tetralogy of Fallot</i>	616	21	0.9 (0.6, 1.5)	83	---	---
<i>d-transposition of the great arteries</i>	448	13	0.8 (0.4, 1.3)	136	8	0.9 (0.4, 1.9)
Atrioventricular septal defect	192	5	0.7 (0.3, 1.7)	83	---	---
LVOTO defects	1232	57	1.2 (0.9, 1.7)	460	33	1.1 (0.8, 1.6)
<i>Hypoplastic left heart syndrome</i>	378	19	1.4 (0.8, 2.2)	112	9	1.3 (0.7, 2.6)
<i>Coarctation of the aorta</i>	643	31	1.3 (0.9, 1.9)	198	11	0.9 (0.5, 1.6)
<i>Aortic valve stenosis</i>	272	7	0.7 (0.3, 1.4)	59	---	---
RVOTO defects	1089	44	1.1 (0.8, 1.5)	370	28	1.2 (0.8, 1.8)
<i>Pulmonary valve stenosis</i>	795	37	1.2 (0.9, 1.7)	227	15	1.1 (0.6, 1.8)
<i>Ebstein malformation</i>	108	4	1.0 (0.4, 2.7)	40	---	---
<i>Pulmonary atresia</i>	144	4	0.7 (0.3, 1.9)	94	---	---
Total anomalous pulmonary venous return	160	6	1.0 (0.4, 2.2)	35	---	---

Reference group is women with untreated first trimester nausea and vomiting of pregnancy (NVP)

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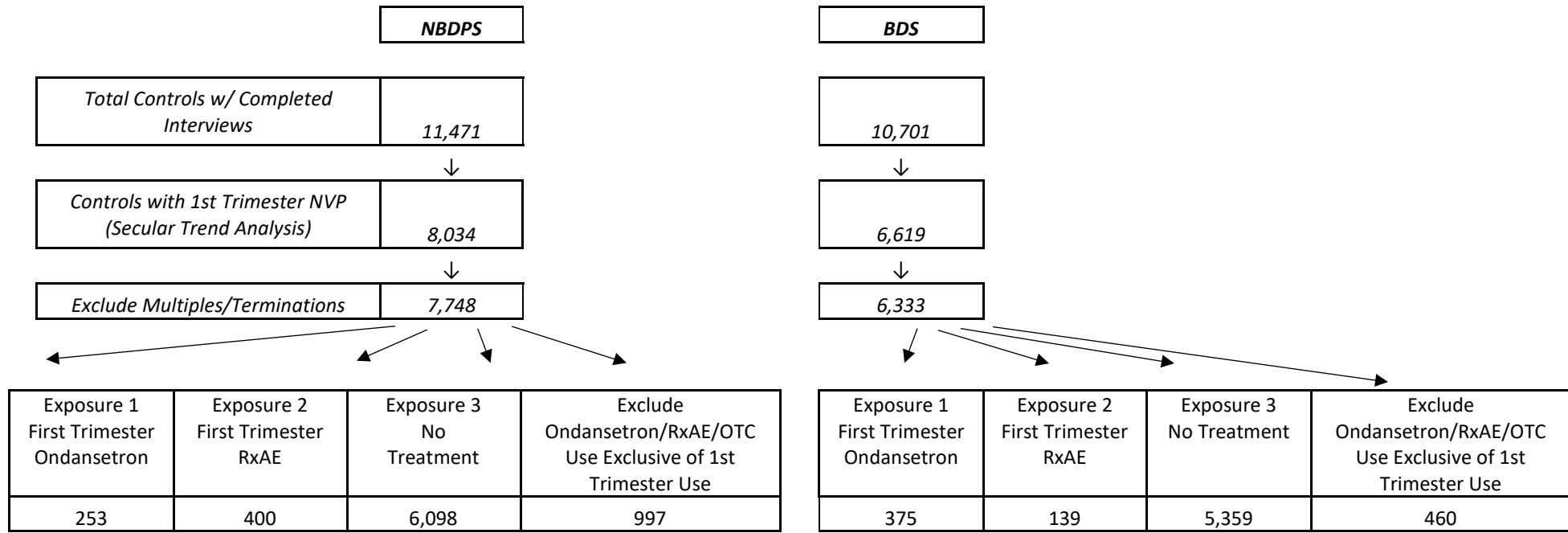
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aOR: adjusted odds ratio; CI: confidence interval; RxAE: Other prescription antiemetics; VSD: ventricular septal defect; ASD: atrial septal defect; LVOTO: left ventricular outflow tract obstruction; RVOTO: right ventricular outflow tract obstruction n/c: not collected

[†]Restricted to male controls only (NBDPS: Total n=1665, with 161 and 2688 ondansetron exposed and unexposed, respectively; BDS: Total n=2910, with 161 and 2688 ondansetron exposed and unexposed, respectively)

[‡]Includes VSD perimembranous, muscular, not otherwise specified

Appendix 4. Exclusion Criteria and Sample Size Flow Chart.



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Appendix 5. Sensitivity Analyses, CP: Odds Ratios and 95% Confidence Intervals for Ondansetron, Other Prescription Anti-Emetics (RxAEs), and Cleft Palate

Only, NBDPS (2005-2011) and BDS (1997-2014)

	NBDPS (2005-2011)					BDS (1997-2014)				
	Total Cases	Ondansetron		RxAEs		Total Cases	Ondansetron		RxAEs	
		No. Exposed	aOR (95 % CI) †	No. Exposed	aOR (95 % CI) †		No. Exposed	aOR (95 % CI) †	No. Exposed	aOR (95 % CI) †
Primary Analysis	418	40	1.6 (1.1, 2.4)	31	1.2 (0.8, 1.8)	287	11	0.5 (0.3, 1.0)	9	1.5 (0.7, 3.0)
<i>Shortened Exposure Window 60 d after conception/70 d after LMP</i>	396	34	1.9 (1.3, 2.8)	15	0.9 (0.5, 1.6)	277	8	0.5 (0.2, 1.0)	2 [‡]	
<i>Excluding Pierre Robin Sequence</i>	335	34	1.6 (1.1, 2.4)	23	1.1 (0.7, 1.8)	260	10	0.5 (0.3, 1.1)	9	1.6 (0.8, 3.3)
<i>Isolated CP</i>	346	33	1.6 (1.1, 2.4)	29	1.4 (0.9, 2.1)	188	6	0.5 (0.2, 1.0)	3 [‡]	
		Ondansetron Only		Ondansetron + RxAEs			Ondansetron Only		Ondansetron + RxAEs	
	Total Cases	No. Exposed	aOR (95 % CI)	No. Exposed	aOR (95 % CI)		No. Exposed	aOR (95 % CI)	No. Exposed	aOR (95 % CI)
<i>Exclusive vs. Combined Use</i>	418	34	1.8 (1.2, 2.7)	6	0.9 (0.4, 2.3)	287	7	0.4 (0.2, 0.9)	4	0.9 (0.3, 2.6)

† Adjusted for maternal age, education, folic acid use, year, and study site

‡ Adjusted ORs not calculated for specified category when <4 exposed subjects

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Appendix 6. Sensitivity Analyses, Renal Agenesis/Dysgenesis: Odds Ratios and 95% Confidence Intervals for Ondansetron and Renal Agenesis/Dysgenesis, BDS (1997-2014) [†]

	BDS (1997-2014)				
	Total Cases	Ondansetron		RxAEs	
		No. Exposed	aOR (95 % CI)	No. Exposed	aOR (95 % CI)
Primary Analysis	159	22	1.8 (1.1, 3.0)	2 [‡]	
<i>Limited to cases with medical record confirmation</i>	151	22	1.9 (1.2, 3.1)	2 [‡]	
<i>Isolated only</i>	65	13	2.6 (1.3, 4.9)	2 [‡]	
<i>Bilateral only</i>	11	2 [‡]		0 [‡]	

aOR: Adjusted for maternal age, education, folic acid use, year, and study site

[†]Fewer than 100 cases in NBDPS

[‡]Adjusted ORs not calculated for specified category when <4 exposed subjects

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