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Risk of Selected Birth Defects with Prenatal Illicit Drug Use, Hawaii, 1986–2002

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The literature on the association between prenatal illicit drug use and birth defects is inconsistent. The objective of this study was to determine the risk of a variety of birth defects with prenatal illicit drug use. Data were derived from an active, population-based adverse pregnancy outcome registry. Cases were all infants and fetuses with any of 54 selected birth defects delivered during 1986–2002. The prenatal methamphetamine, cocaine, or marijuana use rates were calculated for each birth defect and compared to the prenatal use rates among all deliveries. Among all deliveries, the prenatal use rate was 0.52% for methamphetamine, 0.18% for cocaine, and 0.26% for marijuana. Methamphetamine rates were significantly higher than expected for 14 (26%) of the birth defects. Cocaine rates were significantly higher than expected for 13 (24%) of the birth defects. Marijuana rates were significantly higher than expected for 21 (39%) of the birth defects. Increased risk for the three drugs occurred predominantly among birth defects associated with the central nervous system, cardiovascular system, oral clefts, and limbs. There was also increased risk of marijuana use among a variety of birth defects associated with the gastrointestinal system. Prenatal uses of methamphetamine, cocaine, and marijuana are all associated with increased risk of a variety of birth defects. The affected birth defects are primarily associated with particular organ systems.

It is estimated that hundreds of thousands of women use illicit drugs during pregnancy each year in the United States (Hutchins, 1997). Studies have varied widely in the reported prevalence of illicit drug use during pregnancy due to differences in population size, population studied, and study design (Derauf et al., 2003; Norton-Hawk, 1997). Prenatal illicit drug use has been associated with preterm delivery; decreased birth weight, length, and head circumference; and adverse neurobehavioral characteristics shortly after birth, such as withdrawal symptoms (e.g., irritability, tremors, and feeding problems) (Behnke et al., 2001; Cosden et al., 1997; Holzman & Paneth, 1994; Ostrea et al., 1992; Chouteau et al., 1988; Little et al., 1988).

Studies that examine the impact of illicit drug use during pregnancy are often subject to certain limitations (Cosden et al., 1997; Hutchins, 1997; Norton-Hawk, 1997). Individuals who use one illicit drug frequently use other illicit drugs. Thus it is difficult to elicit whether the observed effects are due to a specific drug. Similarly, woman who use illicit drugs during pregnancy may also have other adverse health behaviors or inadequate prenatal care that could account for the observed outcomes.

Another difficulty is the identification of the illicit drug exposure. The two main methods for identification of illicit drug use are through self-report or through toxicology tests, neither of which is ideal. Individuals might be reluctant to report illicit drug use because of the negative moral connotations associated with the practice as well as potential legal ramifications. For the same reasons, individuals may be reluctant to undergo toxicology tests. Furthermore, toxicology tests only provide information on recent illicit drug use. Since both methods of identifying illicit drug exposure have limitations and one may not be superior to the other, it was suggested that both be used together in order to obtain a more accurate estimate of illicit drug use (Christmas et al., 1992).

A number of studies investigated whether prenatal illicit drug use causes birth defects. Various studies reported that maternal cocaine use increased risk of microcephaly, cardiac defects, situs inversus, ventricular septal defect, atrial septal defect, endocardial cushion defect, genitourinary defects, and gastroschisis (Abe et al., 2003; Ferencz et al., 1997a, 1997b, 1997c; Battin et al., 1995; Torfs et al., 1994; Lipshultz et al., 1991; Martin & Edmonds, 1991). Prenatal

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marijuana use was associated with ventricular septal defect, Ebstein anomaly, gastroschisis, and limb–body wall complex (Wlliams et al., 2004; Luehr et al., 2002; Ferencz et al., 1997e; Correa-Villasenor et al., 1994; Torfs et al., 1994). Maternal methamphetamine or amphetamine use has been reported to increase risk of cardiac defects, musculoskeletal defects, and gastroschisis (McElhatton et al., 2000; Torfs et al., 1994). However, other research observed no association between birth defects and maternal use of illicit drugs in general (Frey & Hauser, 2003; Hussain et al., 2002; Croen et al., 2000; Penman et al., 1998; Li et al., 1995), cocaine (Kuehl & Loffredo, 2002; Beaty et al., 2001; Behnke et al., 2001; Gardner et al., 1998; Ferencz et al., 1997d; Hume et al., 1997; Shaw et al., 1996; Martin & Khoury, 1992; Martin et al., 1992; Adams et al., 1989), marijuana (Steinberger et al., 2002; Beaty et al., 2001; Ferencz et al., 1997d; Shaw et al., 1996; Adams et al., 1989), or methamphetamine or amphetamine (Shaw et al., 1996; Little et al., 1988).

Much of the published research on prenatal illicit drug use and birth defects were case reports, involved a small number of cases, were not population-based, or focused on only one or a few particular birth defects. The intent of the current investigation was to evaluate the relationship between use of methamphetamine, cocaine, and marijuana during pregnancy and a variety of birth defects using population-based data from over 300,000 live births.

METHODS

This retrospective study used data from the Hawaii Birth Defects Program (HBDP), a statewide, population-based registry for adverse pregnancy outcomes (National Birth Defects Prevention Network, 2004). The HBDP includes all infants and fetuses of any pregnancy outcome (live births, fetal deaths, and elective terminations) of any gestational age where the delivery occurred in Hawaii and a reportable birth defect, neoplasm, congenital infection, or prenatal illicit drug use was identified between conception and 1 yr after delivery. Trained HBDP staff collected information on eligible subjects through review of medical records at all delivery and tertiary care pediatric hospitals, facilities that perform elective terminations secondary to prenatal diagnosis of birth defects, genetic counseling centers, cytogenetic laboratories, and all but one of the prenatal ultrasound facilities in Hawaii. Through this multiple source system, ascertainment of infants and fetuses diagnosed with eligible conditions (at least for birth defects, neoplasm, and congenital infections) is believed to be as complete as possible because an eligible infant or fetus missed through one ascertainment source is likely to be identified through another. However, independent verification of this assertion has not been documented.

In order to select which medical records to review, the HBDP provides each health care facility with a list of International Classification of Diseases Ninth Revision (ICD-9) codes that designate conditions of interest to the HBDP. Included on this list are the ICD-9 codes for birth defects (mainly 740–759.9) and for noxious influences affecting the fetus via the placenta or breast milk (760.70–760.79). The first range of codes was used to identify infants and fetuses with birth defects, while the latter range of codes was used to identify illicit drug use during pregnancy.

A diagnosis of illicit drug use during pregnancy was based on any mention of illicit drug use during pregnancy in the medical record or a positive toxicology screen for the mother or infant during or shortly after delivery. In the HBDP database, for verification of illicit drug use a positive toxicology screen is considered to be superior to mention in the medical record. So if an illicit drug has a positive toxicology screen and is mentioned in the medical record, the HBDP database only notes that there was a positive toxicology screen. As a result, there is no way to distinguish those instances where the illicit drug use was based on both methods from those instances where the drug use was based solely on a positive toxicology screen.

Cases for the current investigation consisted of all HBDP infants and fetuses delivered during 1986–2002 with a report of prenatal illicit drug use involving methamphetamine, cocaine, or marijuana or a diagnosis of any of 54 selected birth defects. The three illicit drugs were chosen because they were the drugs most commonly reported in prenatal illicit drug use in Hawaii. The particular birth defects were chosen because they were (1) relatively common defects, (2) easy to diagnose, and/or (3) were associated with increased morbidity or mortality. These 54 birth defects are listed in Tables 1–3. All pregnancy outcomes (live births, fetal deaths, elective terminations) were included because in Hawaii a large proportion of fetuses identified with certain types of birth defects do not result in live birth (Forrester & Merz, 2004; Forrester et al., 1998).

The rate of prenatal use of methamphetamine, cocaine, and marijuana was calculated among the population using the number of live births reported to the Hawaii Department of Health as a denominator. Fetal deaths and elective terminations were not included in the denominators because it is not believed that such pregnancy outcomes are accurately reported to the Department of Health.

The rate of each of the 3 illicit drugs was then calculated for each of the 54 selected birth defects. A portion of mothers used two or more of the illicit drugs investigated during a given pregnancy. These mothers were included in all of the relevant analyses. For example, if the mother used methamphetamine and cocaine, the mother was included in the analysis of methamphetamine and the analysis of cocaine. However, in an effort to minimize confounding by associated illicit drugs, the analyses were also performed using those cases where only one of the illicit drugs was reported to have been used.

TABLE 1

Rate of Prenatal Methamphetamine Use Among Infants and Fetuses With Selected Birth Defects, Hawaii, 1986–2002

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Anencephaly	118	1	0.85	1.64	0.04–9.29	1	0.85	2.16	0.05–12.28
Spina bifida	144	0	0.00	0.00	0.00–5.01	0	0.00	0.00	0.00–6.62
Encephalocele	63	1	1.59	3.06	0.08–17.70	1	1.59	4.05	0.10–23.39
Holoprosencephaly	38	2	5.26	10.16	1.19–39.30	1	2.63	6.71	0.17–39.72
Hydrocephaly	353	5	1.42	2.73	0.88–6.44	4	1.13	2.89	0.78–7.47
Microcephaly	328	16	4.88	9.41	5.32–16.52	14	4.27	10.89	5.88–18.53
Anophthalmia/microphthalmia	101	6	5.94	11.46	4.11–25.83	3	2.97	7.58	1.54–22.78
Cataract	39	0	0.00	0.00	0.00–19.15	0	0.00	0.00	0.00–25.30
Glaucoma	11	0	0.00	0.00	0.00–76.90	0	0.00	0.00	0.00–101.62
Anotia/microtia	120	3	2.50	4.82	0.98–14.44	3	2.50	6.38	1.30–19.09
Truncus arteriosus	21	0	0.00	0.00	0.00–37.06	0	0.00	0.00	0.00–48.98
Transposition of great arteries	136	4	2.94	5.68	1.53–14.87	4	2.94	7.50	2.01–19.65
Tetralogy of Fallot	123	3	2.44	4.71	0.96–14.08	2	1.63	4.15	0.50–15.30
Single ventricle	28	2	7.14	13.79	1.59–54.67	2	7.14	18.22	2.10–72.24
Ventricular septal defect	1331	27	2.03	3.91	2.57–5.72	16	1.20	3.07	1.75–5.00
Atrial septal defect	686	16	2.33	4.50	2.56–7.36	10	1.46	3.72	1.78–6.88
Endocardial cushion defect	74	2	2.70	5.22	0.62–19.52	2	2.70	6.89	0.82–25.80
Pulmonary valve atresia/stenosis	293	3	1.02	1.98	0.41–5.83	2	0.68	1.74	0.21–6.35
Tricuspid valve atresia/stenosis	53	2	3.77	7.28	0.86–27.64	1	1.89	4.81	0.12–28.00
Ebstein's anomaly	16	1	6.25	12.06	0.29–77.64	1	6.25	15.94	0.38–102.61
Aortic valve stenosis	38	1	2.63	5.08	0.13–30.06	1	2.63	6.71	0.17–39.72
Hypoplastic left heart syndrome	52	0	0.00	0.00	0.00–14.19	0	0.00	0.00	0.00–18.75
Coarctation of aorta		0	0.00	0.00	0.00–9.73	0	0.00	0.00	0.00–12.86
Interrupted aortic arch	14	0	0.00	0.00	0.00–58.18	0	0.00	0.00	0.00–76.89
Anomalous pulmonary venous return	43	0	0.00	0.00	0.00–17.29	0	0.00	0.00	0.00–22.85
Choanal atresia/stenosis	39	0	0.00	0.00	0.00–19.15	0	0.00	0.00	0.00–25.30
Cleft palate	228	8	3.51	6.77	2.89–13.57	6	2.63	6.71	2.44–14.84
Cleft lip with/without cleft palate	410	10	2.44	4.71	2.24–8.75	5	1.22	3.11	1.01–7.32
Esophageal atresia or tracheoesophageal fistula	69	1	1.45	2.80	0.07–16.11	1	1.45	3.70	0.09–21.29
Pyloric stenosis	255	4	1.57	3.03	0.82–7.85	2	0.78	2.00	0.24–7.30
Small-intestinal atresia/stenosis	89	3	3.37	6.51	1.32–19.64	2	2.25	5.73	0.68–21.32
Anal, rectal, and large-intestinal atresia/stenosis	162	3	1.85	3.57	0.73–10.63	2	1.23	3.15	0.38–11.56

(*Continued*)

TABLE 1
(*Continued*)

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Hirschsprung's disease	69	0	0.00	0.00	0.00–10.60	0	0.00	0.00	0.00–14.01
Biliary atresia	34	0	0.00	0.00	0.00–22.12	0	0.00	0.00	0.00–29.23
Malrotation of intestines	91	0	0.00	0.00	0.00–7.98	0	0.00	0.00	0.00–10.55
Hypospadias and epispadias	856	6	0.70	1.35	0.50–2.96	5	0.58	1.49	0.48–3.49
Renal agenesis or hypoplasia	146	1	0.68	1.32	0.03–7.48	0	0.00	0.00	0.00–6.53
Cystic kidney	144	1	0.69	1.34	0.03–7.59	1	0.69	1.77	0.05–10.03
Obstructive genitourinary defect	455	4	0.88	1.70	0.46–4.37	3	0.66	1.68	0.35–4.95
Bladder exstrophy	9	0	0.00	0.00	0.00–97.78	0	0.00	0.00	0.00–129.21
Persistent cloaca	5	0	0.00	0.00	0.00–210.61	0	0.00	0.00	0.00–278.32
Congenital hip dislocation	312	3	0.96	1.86	0.38–5.47	3	0.96	2.45	0.50–7.23
Polydactyly	568	11	1.94	3.74	1.86–6.74	9	1.58	4.04	1.84–7.73
Syndactyly	276	7	2.54	4.89	1.95–10.22	4	1.45	3.70	1.00–9.57
Reduction deformity of upper limbs	115	3	2.61	5.03	1.02–15.09	0	0.00	0.00	0.00–8.31
Reduction deformity of lower limbs	47	2	4.26	8.21	0.97–31.36	0	0.00	0.00	0.00–20.82
Craniosynostosis	159	0	0.00	0.00	0.00–4.53	0	0.00	0.00	0.00–5.99
Diaphragmatic hernia	78	1	1.28	2.47	0.06–14.20	0	0.00	0.00	0.00–12.35
Omphalocele	90	1	1.11	2.14	0.05–12.26	1	1.11	2.83	0.07–16.20
Gastroschisis	109	1	0.92	1.77	0.04–10.07	1	0.92	2.34	0.06–13.31
Situs inversus	35	2	5.71	11.03	1.29–42.93	2	5.71	14.57	1.70–56.73
Trisomy 21	479	6	1.25	2.42	0.88–5.30	6	1.25	3.19	1.17–7.01
Trisomy 13	62	0	0.00	0.00	0.00–11.83	0	0.00	0.00	0.00–15.64
Trisomy 18	152	1	0.66	1.27	0.03–7.18	1	0.66	1.68	0.04–9.49
Total live births	316,508	1640	0.52	ref		1241	0.39	ref	

Note. A delivery with more than one structural birth defect will be included in all relevant categories.

[a]Total use = all cases of methamphetamine use. Isolated use = cases of methamphetamine use excluding those cases where cocaine or marijuana were also used.

[b]Ratio of the rate of illicit drug use among birth defect cases to the rate of illicit drug use among all deliveries.

[c]CI = confidence interval.

TABLE 2
Rate of Prenatal Cocaine Use Among Infants and Fetuses With Selected Birth Defects, Hawaii, 1986–2002

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Anencephaly	118	0	0.00	0.00	0.00–17.85	0	0.00	0.00	0.00–30.64
Spina bifida	144	0	0.00	0.00	0.00–14.59	0	0.00	0.00	0.00–25.04
Encephalocele	63	0	0.00	0.00	0.00–33.90	0	0.00	0.00	0.00–58.19
Holoprosencephaly	38	0	0.00	0.00	0.00–57.31	0	0.00	0.00	0.00–98.37
Hydrocephaly	353	4	1.13	6.37	1.73–16.46	2	0.57	5.47	0.66–19.90
Microcephaly	328	2	0.61	3.43	0.41–12.48	1	0.30	2.94	0.07–16.51
Anophthalmia/microphthalmia	101	2	1.98	11.13	1.33–41.27	1	0.99	9.55	0.24–54.45
Cataract	39	1	2.56	14.41	0.36–85.18	1	2.56	24.74	0.61–146.22
Glaucoma	11	0	0.00	0.00	0.00–223.99	0	0.00	0.00	0.00–384.47
Anotia/microtia	120	0	0.00	0.00	0.00–17.55	0	0.00	0.00	0.00–30.12
Truncus arteriosus	21	0	0.00	0.00	0.00–107.96	0	0.00	0.00	0.00–185.31
Transposition of great arteries	136	2	1.47	8.27	0.99–30.44	2	1.47	14.19	1.70–52.26
Tetralogy of Fallot	123	3	2.44	13.71	2.79–41.02	1	0.81	7.85	0.20–44.53
Single ventricle	28	0	0.00	0.00	0.00–79.17	0	0.00	0.00	0.00–135.88
Ventricular septal defect	1331	20	1.50	8.45	5.14–13.10	14	1.05	10.15	5.53–17.09
Atrial septal defect	686	9	1.31	7.38	3.36–14.08	5	0.73	7.03	2.28–16.49
Endocardial cushion defect	74	0	0.00	0.00	0.00–28.74	0	0.00	0.00	0.00–49.32
Pulmonary valve atresia/stenosis	293	5	1.71	9.59	3.09–22.64	5	1.71	16.47	5.31–38.87
Tricuspid valve atresia/stenosis	53	1	1.89	10.61	0.26–61.71	1	1.89	18.21	0.45–105.93
Ebstein's anomaly	16	0	0.00	0.00	0.00–145.77	0	0.00	0.00	0.00–250.21
Aortic valve stenosis	38	0	0.00	0.00	0.00–57.31	0	0.00	0.00	0.00–98.37
Hypoplastic left heart syndrome	52	0	0.00	0.00	0.00–41.33	0	0.00	0.00	0.00–70394
Coarctation of aorta	75	2	2.67	14.99	1.78–56.07	2	2.67	25.73	3.06–96.25
Interrupted aortic arch	14	0	0.00	0.00	0.00–169.48	0	0.00	0.00	0.00–290.90
Anomalous pulmonary venous return	43	0	0.00	0.00	0.00–50.36	0	0.00	0.00	0.00–86.44
Choanal atresia/stenosis	39	0	0.00	0.00	0.00–55.77	0	0.00	0.00	0.00–95.73
Cleft palate	228	2	0.88	4.93	0.59–18.02	2	0.88	8.46	1.02–30.93
Cleft lip with/without cleft palate	410	6	1.46	8.23	3.00–18.06	2	0.49	4.71	0.57–17.11
Esophageal atresia or tracheoesophageal fistula	69	1	1.45	8.15	0.20–46.93	1	1.45	13.98	0.35–80.55
Pyloric stenosis	255	3	1.18	6.61	1.36–19.55	1	0.39	3.78	0.10–21.27

(*Continued*)

TABLE 2
(*Continued*)

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Small-intestinal atresia/stenosis	89	1	1.12	6.32	0.16–36.11	1	1.12	10.84	0.27–61.98
Anal, rectal, and large-intestinal atresia/stenosis	162	1	0.62	3.47	0.09–19.61	1	0.62	5.96	0.15–33.66
Hirschsprung's disease	69	0	0.00	0.00	0.00–30.87	0	0.00	0.00	0.00–52.99
Biliary atresia	34	1	2.94	16.53	0.41–98.57	1	2.94	28.38	0.70–169.18
Malrotation of intestines	91	0	0.00	0.00	0.00–23.26	0	0.00	0.00	0.00–39.92
Hypospadias and epispadias	856	1	0.12	0.66	0.02–3.67	1	0.12	1.13	0.03–6.30
Renal agenesis or hypoplasia	146	1	0.68	3.85	0.10–21.79	1	0.68	6.61	0.17–37.41
Cystic kidney	144	2	1.39	7.81	0.94–28.72	2	1.39	13.40	1.61–49.30
Obstructive genitourinary defect	455	4	0.88	4.94	1.34–12.74	3	0.66	6.36	1.30–18.71
Bladder exstrophy	9	0	0.00	0.00	0.00–284.82	0	0.00	0.00	0.00–488.88
Persistent cloaca	5	0	0.00	0.00	0.00–613.50	0	0.00	0.00	0.00–1053.04
Congenital hip dislocation	312	2	0.64	3.60	0.44–13.13	1	0.32	3.09	0.08–17.36
Polydactyly	568	5	0.88	4.95	1.60–11.62	5	0.88	8.49	2.75–19.94
Syndactyly	276	5	1.81	10.18	3.28–24.06	3	1.09	10.49	2.15–30.97
Reduction deformity of upper limbs	115	4	3.48	19.55	5.24–51.44	3	2.61	25.17	5.12–75.43
Reduction deformity of lower limbs	47	1	2.13	11.96	0.30–69.98	0	0.00	0.00	0.00–78.79
Craniosynostosis	159	0	0.00	0.00	0.00–13.20	0	0.00	0.00	0.00–22.65
Diaphragmatic hernia	78	1	1.28	7.21	0.18–41.35	0	0.00	0.00	0.00–46.73
Omphalocele	90	1	1.11	6.25	0.16–35.70	0	0.00	0.00	0.00–40.37
Gastroschisis	109	1	0.92	5.16	0.13–29.35	1	0.92	8.85	0.22–50.37
Situs inversus	35	0	0.00	0.00	0.00–62.49	0	0.00	0.00	0.00–107.26
Trisomy 21	479	0	0.00	0.00	0.00–4.35	0	0.00	0.00	0.00–7.46
Trisomy 13	62	1	1.61	9.07	0.23–52.42	1	1.61	15.56	0.39–89.98
Trisomy 18	152	0	0.00	0.00	0.00–13.81	0	0.00	0.00	0.00–23.71
Total live births	316,508	563	0.18	ref		328	0.10	ref	

Note. A delivery with more than one structural birth defect will be included in all relevant categories.

[a]Total use = all cases of cocaine use. Isolated use = cases of cocaine use excluding those cases where methamphetamine or marijuana were also used.

[b]Ratio of the rate of illicit drug use among birth defect cases to the rate of illicit drug use among all deliveries.

[c]CI = confidence interval.

TABLE 3

Rate of Prenatal Marijuana Use Among Infants and Fetuses With Selected Birth Defects, Hawaii, 1986–2002

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Anencephaly	118	0	0.00	0.00	0.00–12.14	0	0.00	0.00	0.00–26.66
Spina bifida	144	0	0.00	0.00	0.00–12.57	0	0.00	0.00	0.00–21.79
Encephalocele	63	3	4.76	18.20	3.66–55.68	3	4.76	39.98	8.03–122.29
Holoprosencephaly	38	2	5.26	20.12	2.35–77.85	1	2.63	22.09	0.55–130.76
Hydrocephaly	353	8	2.27	8.66	3.71–17.26	7	1.98	16.65	6.65–34.66
Microcephaly	328	8	2.44	9.32	3.99–18.59	5	1.52	12.80	4.13–30.17
Anophthalmia/microphthalmia	101	3	2.97	11.35	2.30–34.14	1	0.99	8.31	0.21–47.38
Cataract	39	0	0.00	0.00	0.00–37.92	0	0.00	0.00	0.00–83.29
Glaucoma	11	0	0.00	0.00	0.00–152.30	0	0.00	0.00	0.00–334.50
Anotia/microtia	120	2	1.67	6.37	0.76–23.52	2	1.67	13.99	1.68–51.66
Truncus arteriosus	21	0	0.00	0.00	0.00–73.41	0	0.00	0.00	0.00–161.22
Transposition of great arteries	136	1	0.74	2.81	0.07–15.93	1	0.74	6.17	0.16–34.98
Tetralogy of Fallot	123	3	2.44	9.32	1.90–27.89	2	1.63	13.65	1.64–50.37
Single ventricle	28	0	0.00	0.00	0.00–53.83	0	0.00	0.00	0.00–118.22
Ventricular septal defect	1331	25	1.88	7.18	4.63–10.65	14	1.05	8.83	4.82–14.87
Atrial septal defect	686	12	1.75	6.69	3.44–11.76	5	0.73	6.12	1.98–14.35
Endocardial cushion defect	74	0	0.00	0.00	0.00–19.54	0	0.00	0.00	0.00–42.91
Pulmonary valve atresia/stenosis	293	5	1.71	6.52	2.10–16.40	4	1.37	11.46	3.10–29.66
Tricuspid valve atresia/stenosis	53	1	1.89	7.21	0.18–41.96	0	0.00	0.00	0.00–60.52
Ebstein's anomaly	16	0	0.00	0.00	0.00–99.12	0	0.00	0.00	0.00–217.69
Aortic valve stenosis	38	1	2.63	10.06	0.25–59.54	1	2.63	22.09	0.55–130.76
Hypoplastic left heart syndrome	52	2	3.85	14.70	1.74–55.85	2	3.85	32.29	3.81–122.65
Coarctation of aorta	75	1	1.33	5.10	0.13–29.28	1	1.33	11.19	0.28–64.30
Interrupted aortic arch	14	0	0.00	0.00	0.00–115.24	0	0.00	0.00	0.00–253.09
Anomalous pulmonary venous return	43	0	0.00	0.00	0.00–34.24	0	0.00	0.00	0.00–75.20
Choanal atresia/stenosis	39	0	0.00	0.00	0.00–37.92	0	0.00	0.00	0.00–83.29
Cleft palate	228	6	2.63	10.06	3.65–22.24	4	1.75	14.73	3.98–38.23
Cleft lip with/without cleft palate	410	7	1.71	6.53	2.61–13.57	4	0.98	8.19	2.22–21.13
Esophageal atresia or tracheoesophageal fistula	69	0	0.00	0.00	0.00–20.99	0	0.00	0.00	0.00–46.11
Pyloric stenosis	255	5	1.96	7.50	2.41–17.72	4	1.57	13.17	3.56–34.13
Small-intestinal atresia/stenosis	89	2	2.25	8.59	1.02–31.95	1	1.12	9.43	0.24–53.93
Anal, rectal, and large-intestinal atresia/stenosis	162	3	1.85	7.08	1.46–21.06	2	1.23	10.36	1.25–38.05
Hirschsprung's disease	69	0	0.00	0.00	0.00–20.99	0	0.00	0.00	0.00–46.11
Biliary atresia	34	0	0.00	0.00	0.00–43.81	0	0.00	0.00	0.00–96.21
Malrotation of intestines	91	1	1.10	4.20	0.11–24.00	1	1.10	9.23	0.23–52.71

(*Continued*)

TABLE 3
(*Continued*)

Birth defect	Total cases	Total use[a]	Rate (%)	Rate ratio[b]	95% CI[c]	Isolated use[a]	Rate (%)	Rate ratio[b]	95% CI[c]
Hypospadias and epispadias	856	4	0.47	1.79	0.49–4.59	3	0.35	2.94	0.61–8.63
Renal agenesis or hypoplasia	146	2	1.37	5.24	0.63–19.26	1	0.68	5.75	0.15–32.55
Cystic kidney	144	1	0.69	2.65	0.07–15.03	1	0.69	5.83	0.15–33.00
Obstructive genitourinary defect	455	7	1.54	5.88	2.35–12.22	5	1.10	9.23	2.98–21.69
Bladder exstrophy	9	0	0.00	0.00	0.00–193.66	0	0.00	0.00	0.00–425.34
Persistent cloaca	5	0	0.00	0.00	0.00–417.15	0	0.00	0.00	0.00–916.18
Congenital hip dislocation	312	1	0.32	1.23	0.03–6.88	0	0.00	0.00	0.00–9.99
Polydactyly	568	8	1.41	5.38	2.31–10.68	6	1.06	8.87	3.24–19.42
Syndactyly	276	13	4.71	18.00	9.47–31.30	8	2.90	24.33	10.40–48.63
Reduction deformity of upper limbs	115	7	6.09	23.27	9.15–49.50	3	2.61	21.90	4.45–65.63
Reduction deformity of lower limbs	47	3	6.38	24.40	4.86–75.80	0	0.00	0.00	0.00–68.55
Craniosynostosis	159	0	0.00	0.00	0.00–8.97	0	0.00	0.00	0.00–19.71
Diaphragmatic hernia	78	0	0.00	0.00	0.00–18.51	0	0.00	0.00	0.00–40.66
Omphalocele	90	1	1.11	4.25	0.11–24.27	0	0.00	0.00	0.00–35.13
Gastroschisis	109	3	2.75	10.52	2.14–31.57	3	2.75	23.11	4.69–69.34
Situs inversus	35	1	2.86	10.92	0.27–64.98	1	2.86	23.99	0.59–142.71
Trisomy 21	479	3	0.63	2.39	0.49–7.04	3	0.63	5.26	1.08–15.46
Trisomy 13	62	0	0.00	0.00	0.00–23.43	0	0.00	0.00	0.00–51.47
Trisomy 18	152	0	0.00	0.00	0.00–9.39	0	0.00	0.00	0.00–20.62
Total live births	316,508	828	0.26	ref		377	0.12	ref	

Note. A delivery with more than one structural birth defect will be included in all relevant categories.

[a]Total use = all cases of marijuana use. Isolated use = cases of marijuana use excluding those cases where methamphetamine or cocaine were also used.

[b]Ratio of the rate of illicit drug use among birth defect cases to the rate of illicit drug use among all deliveries.

[c]CI = confidence interval.

The illicit drug use rates among the birth defects were then compared to the rate among all births by calculating the rate ratio and 95% confidence interval (CI) using Poisson probability.

RESULTS

The HBDP identified 1640 cases of prenatal methamphetamine use, 563 cases of prenatal cocaine use, and 829 cases of prenatal marijuana use among deliveries during 1986–2002. During the same time period, there were 316,508 live births reported in Hawaii. Thus the prenatal use rate was 0.52% for methamphetamine, 0.18% for cocaine, and 0.26% for marijuana. If cases where 2 or more of the illicit drugs were used are excluded, there were 1241 cases of prenatal methamphetamine use, 328 cases of prenatal cocaine use, and 377 cases of prenatal marijuana use. The prenatal use rates for isolated exposures were then 0.39% for methamphetamine, 0.10% for cocaine, and 0.12% for marijuana.

During this 17-yr time period, there were 7293 infants and fetuses with one or more of the 54 birth defects of interest. Of these cases, 6545 (89.7%) were live births, 207 (2.8%) fetal deaths, 527 (7.2%) elective terminations, and 14 (0.2%) unknown pregnancy outcome. The live birth rate varied from 16.1% for anencephaly to 100% for cataract, glaucoma, interrupted aortic arch, choanal atresia/stenosis, Hirschsprung's disease, persistent cloaca, and craniosynostosis.

Table 1 contains the prenatal methamphetamine use rate among selected birth defects. Prenatal methamphetamine rates were significantly higher than expected for 14 (26%) of the birth defects. Most of these defects involved the central nervous system (holoprosencephaly, microcephaly), cardiovascular system (transposition of great arteries, single ventricle, ventricular septal defect, atrial septal defect), oral clefts (cleft palate alone, cleft lip with/without cleft palate), and limbs (polydactyly, syndactyly, reduction deformity of upper limbs). Other birth defects with significantly higher than expected prenatal methamphetamine rates were anophthalmia/microphthalmia, small-intestinal atresia/stenosis, and situs inversus. If the analysis was restricted only to those cases where methamphetamine alone was used, then the rates were significantly higher than expected for 12 (22%) of the birth defects (microcephaly, anophthalmia/microphthalmia, anotia/microtia, transposition of great arteries, single ventricle, ventricular septal defect, atrial septal defect, cleft palate alone, cleft lip with/without cleft palate, polydactyly, situs inversus, trisomy 21).

Table 2 presents the prenatal cocaine use rate for the same birth defects. Prenatal cocaine rates were significantly higher than expected for 13 (24%) of the birth defects. These defects were primarily associated with the central nervous system (hydrocephaly), cardiovascular system (tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, coarctation of aorta), oral clefts (cleft lip with/without cleft palate), and limbs (polydactyly, syndactyly, reduction deformity of upper limbs). Other birth defects with significantly higher than expected cocaine rates were anophthalmia/microphthalmia, pyloric stenosis, and obstructive genitourinary defect. If the analysis included only the cases where cocaine alone was reported, then the rates were significantly higher than expected for 11 (20%) of the birth defects (transposition of great arteries, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, coarctation of aorta, cleft palate alone, cystic kidney, obstructive genitourinary defect, polydactyly, syndactyly, reduction deformity of upper limbs).

Table 3 shows the prenatal marijuana use rate for the 54 birth defects. Prenatal marijuana rates were significantly higher than expected for 21 (39%) of the birth defects. The birth defects with greater than expected prenatal marijuana use rates were mainly defects of the central nervous system (encephalocele, holoprosencephaly, hydrocephaly, microcephaly), cardiovascular system (tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome), oral clefts (cleft palate alone, cleft lip with/without cleft palate), gastrointestinal system (pyloric stenosis, small-intestinal atresia/stenosis, anal/rectal/large-intestinal atresia/stenosis), and limbs (polydactyly, syndactyly, reduction deformity of upper limbs, reduction deformity of lower limbs). Other birth defects with significantly increased prenatal marijuana rates were anophthalmia/microphthalmia, obstructive genitourinary defect, and gastroschisis. If the analysis was limited to those cases where marijuana by itself was used, then the rates were significantly higher than expected for 19 (35%) of the birth defects (encephalocele, hydrocephaly, microcephaly, anotia/microtia, tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome, cleft palate alone, cleft lip with/without cleft palate, pyloric stenosis, anal/rectal/large-intestinal atresia/stenosis, obstructive genitourinary defect, polydactyly, syndactyly, reduction deformity of upper limbs, gastroschisis, trisomy 21).

DISCUSSION

Using data from a statewide, population-based registry that covered over 300,000 births and a 17-yr period, this investigation examined the association between over 50 selected birth defects and maternal use of methamphetamine, cocaine, or marijuana during pregnancy. Much of the literature on prenatal illicit drug use and birth defects involved case reports, involved a small number of cases, were not population-based, or focused on only one or a few particular birth defects.

There are various limitations to this investigation. The number of cases for many of the birth defects categories was relatively small, limiting the ability to identify statistically significant differences and resulting in large confidence intervals. In spite of this, a number of statistically significant analyses were identified. Some statistically significant results might

be expected to occur by chance. If 1 in every 20 analyses is expected to result in statistically significant differences solely by chance, then among the 162 analyses performed in this study, 8 would be expected to be statistically significant by chance. However, 48 statistically significant differences were identified. Thus, not all of the statistically significant results are likely to be due to chance.

This study included all pregnancies where methamphetamine, cocaine, or marijuana use was identified through either report in the medical record or positive toxicology test. This was done because neither self-report nor toxicology testing is likely to identify all instances of prenatal illicit drug use (Christmas et al., 1992). In spite of using both methods for determining prenatal illicit drug use, all pregnancies involving methamphetamine, cocaine, or marijuana were not likely to have been identified. The degree of under ascertainment is unknown. A previous study examined the maternal drug use rate around the time of delivery in Hawaii during 1999 (Derauf et al., 2003). This study found 1.4% of the pregnancies involved methamphetamine use and 0.2% involved marijuana use. Among 1999 deliveries, the HBDP identified a prenatal methamphetamine use rate of 0.7% and a marijuana use rate of 0.4%. However, comparisons between the 2 studies should be made with caution because the previous study collected data from a single hospital during only a 2-mo period.

Another limitation is that the present study did not control for potential confounding factors such as maternal demographic characteristics, health behaviors, and prenatal care. Increased risk of birth defects has been associated with inadequate prenatal care (Carmichael et al., 2002), maternal smoking (Honein et al., 2001), and maternal alcohol use (Martinez-Frias et al., 2004). These factors are also found with maternal illicit drug use (Cosden et al., 1997; Hutchins, 1997; Norton-Hawk, 1997). Thus the increased risk of selected birth defects with illicit drug use in this study might actually be due to one of these other underlying factors. Unfortunately, information on some of the potential confounding factors such as socioeconomic status are not collected by the HBDP. Information collected on some other factors such as smoking and alcohol use is suspect because of negative attitudes toward their use during pregnancy. Moreover, the small number of cases among many of the birth defects groups would make controlling for these factors difficult.

Finally, this investigation included use of the illicit drugs at any time during the pregnancy. Most birth defects are believed to occur at 3–8 wk after conception (Makri et al., 2004; Sadler, 2000). In a portion of the cases, the drug use might have occurred at a time when it could not have caused the birth defect. Furthermore, this study does not include information on dose; however, teratogenicity of a substance may depend on its dose (Werler et al., 1990). In spite of the various potential concerns of the present study, data may suggest future areas of investigation where the limitations inherent in the present one are excluded.

This investigation found significantly higher than expected rates for prenatal use of methamphetamine, cocaine, and marijuana among a number of specific birth defects. Although not identical, there were general similarities between the three illicit drugs and the birth defects with which they were associated. Increased rates for methamphetamine, cocaine, and marijuana occurred predominantly among birth defects affecting the central nervous system, cardiovascular system, oral clefts, and limbs. There were also increased rates of marijuana use with a variety of birth defects associated with the gastrointestinal system. With the exception of marijuana and encephalocele, none of illicit drugs were associated with neural-tube defects (anencephaly, spina bifida, encephalocele). The rates of use for the three illicit drugs were not significantly elevated with eye defects other than anophthalmia/microphthalmia, genitourinary defects, and musculoskeletal defects aside from limb defects. In the majority of instances, the associations between particular illicit drugs and birth defects were found whether or not those cases involving use of multiple types of drugs were included. Of the 14 significant associations between methamphetamine and specific birth defects, 10 (71.4%) remained once multiple drug cases were excluded. Corresponding rates were 61.5% (8 of 13) for cocaine and 81.0% (17 of 21) for marijuana.

The similarities in the patterns of birth defects with which methamphetamine, cocaine, and marijuana are associated might suggest that the three drugs exert similar effects on embryonic and fetal development. This might not be expected, considering that the three illicit drugs differ in their mechanisms of action and clinical effects (Leiken & Paloucek, 1998).

Some of the associations between methamphetamine, cocaine, and marijuana observed in the present investigation were previously reported. Other studies observed similar associations, or lack thereof, of methamphetamine or amphetamine with neural-tube defects (Shaw et al., 1996) and cardiovascular and musculoskeletal defects (McElhatton et al., 2000); cocaine with neural-tube defects (Shaw et al., 1996), cardiovascular defects (Lipshultz et al., 1991), ventricular septal defect and atrial septal defect (Ferencz et al., 1997c; Martin & Edmonds, 1991), tricuspid atresia (Ferencz et al., 1997d), craniosynostosis (Gardner et al., 1998), and situs inversus (Kuehl & Loffredo, 2002); and marijuana with neural-tube defects (Shaw et al., 1996), single ventricle (Steinberger et al., 2002), ventricular septal defect (Williams et al., 2004), tricuspid atresia (Ferencz et al., 1997d), and gastroschisis (Torfs et al., 1994).

In contrast, this study differed from other research with respect to their findings regarding methamphetamine or amphetamine and gastroschisis (Torfs et al., 1994); cocaine and microcephaly (Martin & Edmonds, 1991), conotruncal defects (Adams et al., 1989), endocardial cushion defect (Ferencz et al., 1997b), situs inversus (Ferencz et al., 1997a), oral clefts (Beaty et al., 2001), and genitourinary defects (Abe et al., 2003; Battin et al., 1995; Martin & Edmonds, 1991); and marijuana and conotruncal defects (Adams et al., 1989), Ebstein anomaly (Ferencz et al., 1997e; Correa-Villasenor et al., 1994), and oral

clefts (Beaty et al., 2001). The inconsistent findings between this and the other studies could be due to differences in study methodology, case classification, or number of cases.

The mechanisms by which methamphetamine, cocaine, and marijuana might contribute to the rates for birth defects is currently unknown. Any potential explanation would have to take into account the observation that each of the illicit drugs was associated with a variety of specific birth defects affecting different organ systems. This might suggest that these three drugs would need to influence a basic, common factor involved in embryonic development.

Folic acid is involved in nucleic acid synthesis and cellular division (Scholl & Johnson, 2000) and thus would play an important role in the early growth and cellular proliferation of the embryo. Folic acid has been found to prevent a variety of birth defects (Forrester & Merz, 2005). Thus, anything that interferes with the activity of folic acid might be expected to increase the risk for these birth defects. Many of these birth defects were associated with methamphetamine, cocaine, and/or marijuana in the present study. However, two of the birth defects most closely affected by folic acid—anencephaly and spina bifida—were not associated with any of the three illicit drugs.

Vascular disruption has been suggested as a potential cause for a variety of different birth defects such as intestinal atresia/stenosis, limb reduction defects, and gastroschisis. Since cocaine is a vasoconstrictor, it has been hypothesized that cocaine use could increase the risk of these vascular disruption defects (Hume et al., 1997; Martin et al., 1992; Hoyme et al., 1983; de Vries, 1980). Although this investigation found an association between cocaine and limb reduction deformities, no association was found with intestinal atresia/stenosis or gastroschisis.

In conclusion, this study found that prenatal use of methamphetamine, cocaine, or marijuana were associated with increased risk of a variety of birth defects. The affected birth defects were primarily associated with particular organ systems. Because of various limitations of the study, further research is recommended.

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