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Clinical and Risk Factor Analysis of Cloacal Defects in the National Birth Defects Prevention Study

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Abstract

Cloacal exstrophy (CE) and persistent cloaca (PC) (alternatively termed urorectal septum malformation sequence [URSMS]), represent two major cloacal defects (CDs). Clinical characteristics and risk factors often are studied for both defects combined, rather than exploring if these defects have different etiologies. We enumerated clinical features for 47 CE and 54 PC (inclusive of URSMS) cases from the National Birth Defects Prevention Study. Thirty-three CE cases were classified as isolated and 14 as multiple (presence of unassociated major defects); respective totals for PC cases were 26 and 28. We compared selected child and maternal characteristics between 11829 non-malformed controls and CE and PC cases using chi-square or Fisher's exact tests. Compared to controls, CE and PC cases were statistically more likely ($p<0.05$) to be preterm; CE cases were more likely to be multiple births. We conducted logistic regression analysis to estimate odds ratios and 95% confidence intervals for any CD, CE, and PC with selected self-reported maternal pre-pregnancy and periconceptional (one month prior to three months following conception) exposures. In crude and adjusted analyses, we observed significant positive associations for any CD, CE, and PC with use of any fertility medication or assisted reproductive technology procedure. Significant positive associations observed only in crude analyses were any CD with maternal obesity or use of progesterone, any CD and CE with any x-ray, and any CD and PC with use of folate antagonist medications. Our findings provide some of the first insights into potential differing etiologies for CE and PC.

Keywords

cloacal exstrophy; OEIS complex; omphalocele; imperforate anus; persistent cloaca; urorectal septum malformation sequence; population-based study

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INTRODUCTION

Cloacal exstrophy (CE), also known as OEIS complex, represents a combination of defects consisting of omphalocele, exstrophy of the cloaca, imperforate anus, and spinal defects [Carey et al., 1978]. CE may also represent the most severe end of a spectrum of ventral body wall defects that includes bladder exstrophy (BE) [Smith et al., 1992]. Persistent cloaca (PC), alternatively referred to as urorectal septal malformation sequence (URSMS), is characterized by a common cloacal cavity that includes bladder and intestinal elements, usually with imperforate anus without exstrophy [Escobar et al., 1987; Wheeler et al., 1997; Wheeler et al., 2001]. The term persistent cloaca is used to refer to a type of anorectal malformation in females [Holschneider et al., 2005; Peña, 2016]; URSMS (partial) includes males whose cloacal cavity consists of colon or rectum and bladder with a single opening [Wheeler et al., 2001]. Other defects involving the gastrointestinal, skeletal, spinal, and genitourinary systems are reported frequently in CE and PC/URSMS [Martinez-Frias et al., 2001; Keppler-Noreuil et al., 2001; Van der Putte et al., 2008].

Reported prevalence estimates for CE historically ranged from 1/200,000 – 1/400,000 births [Soper and Kilger, 1964; Hurwitz et al., 1987; Martinez-Frias et al., 2001;] however, other reviews reported higher estimates ranging from 1/10,000 – 1/70,000 live births [Hayden et al., 1973; Peterson and Nelson, 1982; Evans et al., 1985; Martinez-Frias et al., 2001; Keppler-Noreuil, 2001; Caton et al., 2007; Feldkamp et al., 2011; Kubota, 2017]. These higher estimates may be due, in part, to improved ascertainment of CE in stillbirths or to prenatal misdiagnosis [Keppler-Noreuil et al., 2007]. PC/URSMS has an estimated prevalence of 1 in 35,000 – 50,000 based upon a small number of population-based studies [Gray et al., 2001; Cushieri et al., 2001; Tennant et al., 2014]. The population-based study by Tennant et al. [2014] in England and Wales reported that most cases of PC/URSMS (partial) were diagnosed with additional structural defects, one in two with renal anomalies, and one in four with gastrointestinal, cardiovascular, or limb anomalies. Additionally, results of a survey of 244 university hospitals and children's hospitals in Japan [Kubota 2017], showed similar findings of associated defects among PC cases.

The etiology for both CE and PC/URSMS remains unknown. Although there have been individual cases of CE with chromosome abnormalities, including trisomy 18 [Carey et al., 1978], 9q24.1-qter deletion [Thauvin-Robinet et al., 2004], 3q12.2-q13.2 deletion [Kosaki et al., 2005], and 1p36.13 deletion [El-Hattab et al., 2010], there has been no single, recurrent chromosome abnormality associated with CE. Similarly for PC/URSMS, there has been no single, recurrent chromosome abnormality, but there have been isolated reports of chromosome rearrangements of 7p and 8q in patients with a syndrome [Miller et al., 1979; Ramos et al., 1992].

Previous array-based molecular analysis, copy number variant (CNV) studies, and selected candidate gene analyses did not reveal any pathogenic alterations associated with CE or PC [Vlangos et al, 2011; Draaken et al., 2013; Reutter et al., 2006; Reutter et al., 2007a; Reutter et al., 2007b; Ludwig et al., 2009b; Jenkins et al., 2007]. A recent CNV study of 17 females with PC identified seven patients with CNVs, two of which were novel, a de novo deletion on 1q32.1q32.3 and a paternally inherited duplication on 16p13.2 [Harrison, Seideman,

Baker, 2014]; however, sequencing of candidate gene *HHAT* in these 17 patients was negative [Harrison, Seideman, Baker, 2014]. Also, a mutation in Uroplakin IIIA (*UPIIIA*) identified in a patient with PC and renal dysplasia was not replicated in a subsequent study of 20 PC patients sequenced for mutations in the *UPIIA, SHH, HNF1B*, and *EFNB2* genes [Jenkins et al., 2005; Jenkins et al., 2007].

The one published whole exome sequencing study of CE, which was conducted in eight child-parent trios, identified variants in three genes – *PRPF38A, PRPF8*, and *SLC20A1* – by *in silico* prediction programs; however, only the *SLC20A1* variant was considered plausible based upon its known expression pattern [Reutter et al., 2016]. Sanger sequencing of additional CE patients did not reveal any potentially causative variants in *SCLC20A1* (Reutter, personal communication). An unpublished whole exome sequencing study in six CE child-parent trios performed through the Center for Mendelian Genomics at the University of Washington did not reveal any plausible candidate genes (Keegan et al, unpublished). Additionally, the few candidate gene and genome-wide association studies performed to date on the bladder exstrophy-epispadias complex (BEEC) – which includes BE, PC, and CE – reported several potential candidate genes, including *ISL1* [Draaken et al., 2015], *p63* [Qi et al., 2013; Wilkins et al., 2012], and *WNT3* [Reutter et al., 2014].

Most cases of CDs occur sporadically and empirical recurrence risk is low. A few reports of recurrence of CE, PC, or associated defects, such as anal atresia, bladder exstrophy, or omphalocele, in families were identified [Smith et al., 1992; Keppler-Noreuil et al., 2001; Gambhir et al., 2008; Aggarwal and Phadke, 2013; Mills and Pergament, 1997] with a higher reported occurrence in monozygotic twins [Koffler et al., 1978; Schinzel et al., 1979; Redman et al., 1981; McLaughlin et al., 1984; Smith et al., 1992; Kramer et al., 1997; Lee et al., 1999; Seibert et al., 2005; Lubusky et al., 2006] and concordant conjoined twins with CE [Metneki and Czeizel, 1989; Goldfischer et al., 1997; Tihtonen et al., 2009] than in singletons. Despite the absence of consistent genetic reports, findings from monozygotic twin studies support a genetic etiology for CE and PC; however, reports of discordant dizygotic twins [Bruch et al., 1996; Achiron et al., 2000] cannot exclude environmental, epigenetic, or somatic mosaic etiologies.

Previous epidemiologic studies have reported clinical findings and possible risk factors for CE [Martinez-Frias et al., 2001; Boyadjiev et al, 2004; Caton et al., 2007; Gambhir et al, 2008], although some of these studies did not analyze CE separately from PC or BE [Boyadjiev et al, 2004; Gambhir et al, 2008; Cushieri et al., 2001]. CE and BE may have different pathogeneses based upon their different clinical characteristics, prevalence, and demographics [Martinez-Frias et al. 2001; Caton et al. 2007]. With regard to CE, associations have been reported with low birth weight, preterm gestation, and twinning [Martinez-Frias et al., 2001; Boyadjiev et al, 2004; Caton et al., 2007; Gambhir et al, 2008] and, also, with maternal use of clomiphene citrate [Reefhuis et al. [2011]. Additionally, possible maternal exposures to diazepam and diphenylhydantoin was thought to be a risk factor in a single case report [Carey et al, 1978].

With the limitations in case definitions used and paucity of risk factors examined in previous epidemiologic studies of CE and PC/URSMS, we conducted a comprehensive clinical and

risk factor analysis of CE and PC (inclusive of URSMS) (henceforth collectively termed cloacal defects [CDs]) using data from the National Birth Defects Prevention Study (NBDPS), a multi-state population-based case-control study. Our study objectives using this systematically identified sample of CD cases were to describe clinical findings for cases, including occurrence and types of other major birth defects, and to examine associations between CDs and selected child and maternal characteristics, as well as maternal pre-pregnancy and periconceptional exposures.

METHODS

The NBDPS examined risk factors for over 30 major birth defects; methodology for the study has been described previously [Yoon et al., 2001; Reefhuis et al., 2015]. Included in the current analyses were cases with one or more eligible defects and unaffected live born controls with estimated dates of deliveries (EDDs) from October 1, 1997-December 31, 2011. Initial NBDPS sites were birth defect surveillance programs in seven states (Arkansas [AR], California [CA], Iowa [IA], Massachusetts [MA], New Jersey [NJ], New York [NY], Texas [TX]), and the Centers for Disease Control and Prevention in Georgia (CDC/GA). In 2003, surveillance programs in two additional states (North Carolina [NC], Utah [UT]) were included in the NBDPS, and data collection ceased in NJ. All participating sites ascertained live births diagnosed with birth defects and all but NJ ascertained fetal deaths (AR, CA, CDC/GA, IA, MA, NC, NY 2000–2011, TX, UT) or elective terminations (AR, CA, CDC/GA, IA, MA 2011, NC, NY 2000–2011, TX, UT). Controls were identified from the same catchment areas as cases and randomly selected from either hospital delivery logs (AR 1997–2000, CA, CDC/GA 1997–2000, NY, TX) or birth certificate files (AR 2000–2011; CDC/GA 2001–2011, IA, MA, NC, NJ, UT). Cases with defects of known or strongly suspected genetic etiology (i.e., single gene disorders, chromosome abnormalities), as well as cases and controls not in the custody of or not residing with their birth mothers or whose birth mothers did not speak English or Spanish were excluded. Each site obtained institutional review board approval for the NBDPS.

Case Classification

Clinical information abstracted from medical records was reviewed by a clinical geneticist at each NBDPS site, and standard definitions were used to determine case classification [Rasmussen et al., 2003]. An expanded version of the British Paediatric Association (BPA) codes (themselves an expansion of the International Classification of Disease Coding Modification Version 9 [ICD-9-CM]) were used to code NBDPS-eligible defects. The BPA code used for CDs, which included CE and PC, was 751.550.

Classification of all NBDPS cases with a CD was performed by two clinicians (KKN, JCC) to confirm diagnosis of CE or PC and assign each case as isolated or multiple (presence of other unassociated major birth defects). The case definition and diagnosis of an isolated or complex sequence CE case required the presence of BE or CE and imperforate anus with either omphalocele or spina bifida. Other associated defects with isolated CE may have included spinal, kidney/urinary tract, gastrointestinal, or ambiguous or incompletely formed genitalia. PC and URSMS were used synonymously in this study, recognizing that URSMS

occurs in males and females, and that PC is used to describe these defects in females. For the purposes of describing our results, the term PC is used to represent the cases of PC and URSMS combined. The case definition for isolated PC required a common cloacal cavity with bladder and intestinal elements (and vaginal elements in the females) invariably accompanied by an anorectal defect, usually imperforate anus, but without exstrophy. An isolated PC case may have included the same associated defects as described for isolated CE. A multiple CE or PC case was defined as the respective primary defect plus other unassociated defects (e.g., congenital heart defects, brain defects, limb defects, craniofacial defects, or lung hypoplasia). All cases of CE diagnosed by physical examination or autopsy were required to have at least an omphalocele, BE, and an anorectal defect. Cases described as probable or possible CE were excluded.

Data Collection

Clinical data collected through medical record abstraction included demographic data, prenatal history, and clinical findings with occurrence and types of presenting birth defects. Structured, computer-assisted telephone interviews were conducted with birth mothers of cases and controls; interviews were conducted from 6 weeks to 2 years following the EDD of the case or control. The maternal interview included, but was not limited to, detailed items about demographic characteristics, pregnancy history, pregnancy intention, use of fertility procedures, medical history, and maternal use of nutritional supplements, medications, tobacco, alcohol, and illicit drugs. For most items, information was collected for each of the three months before pregnancy (B3-B1), each month of the first trimester (M1-M3), and by trimester for the remainder of the pregnancy (T2 and T3). In our analysis, unless otherwise specified, exposures were coded for the periconceptional period (one month before pregnancy [B1] through the third month of pregnancy [M3]).

Statistical Analysis

We analyzed child and maternal characteristics and maternal pre-pregnancy and periconceptional exposures. We compared child and maternal characteristics of controls with those for all CDs combined, CE only, and PC only; analyses were also stratified by isolated or multiple CE or PC phenotypes and compared to controls. Additionally, we compared child and maternal characteristics between CE and PC cases. Characteristics were compared using chi-square or Fisher's exact tests (when expected cell counts <5) to determine statistical differences ($p<0.05$).

Child characteristics compared were sex (female, male), gestational age (<37 weeks, 37–45 weeks), plurality (singleton, multiple), and for CE vs. PC cases only, birth outcome (live birth, stillbirth, elective termination). Maternal characteristics compared were age at delivery (<20 years, 20–34 years, ≥35 years), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), education at delivery (<12 years, 12 years, ≥13 years), study site (AR, CA, CDC/GA, IA, MA, NC, NJ, NY, TX, UT), gravidity (first pregnancy, second pregnancy, third or higher pregnancy), previous miscarriage (yes, no), and planned pregnancy (yes, no, did not care).

Maternal pre-pregnancy exposures examined were use of fertility medication or assisted reproductive technology (ART) procedure, including nonsurgical or surgical procedures (yes, no); chorionic villus sampling (yes, no); body mass index (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2); type I or II diabetes (yes, no), history of hypertension (yes, no); and caffeine consumption (≤10 mgs/day, >10 and <100 mgs/day, ≥100 and <200 mgs/day, ≥200 and <300 mgs/day, ≥300 mgs/day). Maternal periconceptional exposures examined were infection due to a urinary tract infection (UTI) or pelvic inflammatory disease (PID) (yes, no), fever (yes, no), any x-ray (yes, no), progesterone use (yes, no), folic acid-containing supplements (yes, no), vitamin A supplements (yes, no), vasoactive medications (yes, no), folate antagonist medications (yes, no), retinoic acid medications (yes, no), cigarette smoking exposure (none, active smoking only, passive smoking only, active and passive smoking), alcohol consumption (none, yes-no binging, yes-binging [≥4 drinks on one occasion]), and illicit drug use (yes, no). Vasoactive medications examined were decongestants, antimigraine medications, amphetamines, cocaine, bronchodilators, anti-hypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), and other medications with vasoactive components. Folate antagonists used by subject mothers included carbamazepine, cholestyramine resin, methotrexate, sulfasalazine, triamterene, trimethoprim, phenytoin, and phenobarbital. Aminopterin sodium, oxcarbazepine, pyrimethamine, primidone, and valproate sodium also were classified as folate antagonists, but no case or control mother reported use of these medications. The retinoic acid medication examined was Retin-A.

Crude odds ratios (cORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs) were estimated using logistic regression analysis to investigate the associations of any CD, CE, and PC with maternal pre-pregnancy and periconceptional exposures. Adjusted analyses were conducted only for levels of exposures that included at least five exposed case mothers. Exact logistic regression was used for crude and adjusted analyses of the association of a case group with an exposure when at least one level of exposure included fewer than five case mothers. Covariables examined were child sex and plurality, along with maternal age at delivery, race and ethnicity, education at delivery, and study site. Each covariable was added separately to the exposure-only model; covariables that changed the cOR estimate by more than 10% were included in the adjusted model for the respective case group and exposure. No restrictions were placed on the number of covariables that could be included in the adjusted models. Because the focus of our paper was to explore potential exposures for CE and PC singly, we chose not to include an exposure as a covariable in model testing of other exposures. Instead, selected covariables from previous studies of CDs and that preceded the critical fetal developmental period, along with NBDPS study site, were evaluated for inclusion in adjusted analyses. All analyses were conducted using the Statistical Analysis System (SAS) version 9.3 statistical software (SAS institute, Cary, NC).

RESULTS

Clinical and maternal interview data were available for 101 children with CDs and 11,829 control children. Overall, participation in the maternal interview was 67% among case mothers and 64% among control mothers. The median time between EDD and interview date was 11 months for case mothers and 7 months for control mothers.

Of the 101 CD cases, 47 were classified with CE (Isolated=33; Multiple=14) and 54 with PC (Isolated=26; Multiple=28) (Table I). Findings of limb body wall complex (LBWC) were observed for two isolated CE cases, including one with short umbilical cord, and one possible LBWC was observed among isolated PC cases. Among the cases classified as multiple CE, congenital heart defects were most commonly observed followed by limb deficiency defects, specifically tibial agenesis. Among multiple PC cases, congenital heart defects and phenotypes that resembled those in VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and radial limb abnormalities) association were observed most often.

CE and PC had similar spinal, kidney, urinary, and gastrointestinal defects (data not shown). Nearly all (98/101; 98%) CD cases were diagnosed with kidney, bladder, or urinary tract defects (hydronephrosis/hydroureter, agenesis of unilateral kidney, cystic dysplasia of the kidneys, pelvic kidney, horseshoe kidney, single umbilical artery, BE, hemibladders, duplicated collecting system, or fistulas with the rectum, vagina, and urogenital sinus).

Overall, 78 of the 101 (77%) CD cases had a chromosome analysis; all analyses were normal (data not shown). The karyotypes 46,XX and 46,XY were observed equally in CE cases (N=18 each). In PC cases, the 46,XX karyotype was observed in 38 cases, and the 46,XY karyotype was observed in four cases. Among CE cases without chromosome analysis, there were four phenotypic females and three phenotypic males; an additional two CE cases had ambiguous phenotypic sex assignment, and two CE cases had no phenotypic sex assignment. Among PC cases without chromosome analysis, there were eleven phenotypic females and one PC case with ambiguous sex assignment. External genitalia findings in 46,XX individuals included absent or labioscrotal folds; labia that were fused, small, or displaced to one side; and absent, bifid, or large clitoris. Internal genitalia findings in 46,XX individuals included single to absent ovaries and fallopian tubes; absent, bifid, bicornuate, or didelphys uteri; and absent or duplicated vaginas. In 46,XY individuals, external genitalia findings included splayed labioscrotal folds; absent, small, bifid, or duplicated phalli; epispadias; and absent, small, or empty scrotum with cryptorchidism. Internal genitalia findings in 46,XY individuals included urethral atresia and absent, small, or intra-abdominal testes.

Child and Maternal Characteristics

Comparing child characteristics between each case group (any CD, CE, PC) and controls, we observed a female excess for any CD case, accounted for largely by PC (Table II). Children in each case group were statistically more likely ($p<0.05$) to be preterm, and those with any CD and CE were more likely to be from a multiple pregnancy than controls. Differences observed for isolated and multiple CE cases and for isolated and multiple PC cases were similar to those observed for all CE and all PC cases, respectively (data not shown). Comparing CE and PC cases, we observed that PC cases were statistically less likely to be preterm or a multiple pregnancy than CE cases; no statistical difference was observed among birth outcomes between CE and PC cases (data not shown).

Comparing maternal demographic and reproductive history characteristics between each case group and controls, we observed no statistical differences (Table II). Likewise,

comparison of these characteristics did not produce statistical differences between CE and PC cases. No case mother reported a diagnosis of diabetes prior to pregnancy.

Maternal Pre-pregnancy and Periconceptional Exposures

Outcome and exposure model-specific covariables identified for inclusion in adjusted analyses are shown in Table III. Results of crude analysis are presented in Table IV; results of adjusted analysis are reported in text for associations with statistically significant cORs.

Examination of maternal pre-pregnancy exposures in crude logistic regression analysis yielded statistically significant positive associations for any CD, CE, and PC with reported use of any fertility medication or an ART procedure, as well as a statistically significant positive association for any CD with maternal obesity (BMI ≥30.0 kg/m^2) compared to normal weight (18.5–24.9 kg/m^2) (Table IV). The significant, positive associations persisted for use of any fertility medication or an ART procedure with any CD when controlling for child plurality and maternal age at delivery (aOR = 3.2; 95% CI = 1.7–5.9); with CE when controlling for child sex and plurality and maternal age at delivery, race/ethnicity, and education at delivery (aOR = 2.7, 95% CI = 1.0–7.2); and with PC when controlling for child sex and maternal age at delivery (aOR = 3.6; 95% CI = 1.6–8.2) (data not shown). No covariables met the criteria for inclusion in an adjusted model of maternal obesity with any CD.

Examination of maternal periconceptional exposures in crude logistic regression analysis yielded statistically significant positive associations for any CD and CE with any reported x-ray, for any CD with reported use of progesterone, and for any CD and PC with reported use of folate antagonist medications (Table IV). No covariables met the criteria for inclusion in adjusted models of any maternal x-ray with any CD or CE. The significant, positive association observed for maternal use of progesterone with any CD did not persist when controlling for child plurality and maternal age at delivery (aOR = 1.9; 95% CI = 0.8–4.5) (data not shown). There were too few CD and PC cases whose mothers reported use of folate antagonist medications to conduct adjusted analysis on these case groups for this exposure. No case mother reported use of vitamin A supplements or retinoic acid medication.

DISCUSSION

Our population-based case-control study described the clinical features of CDs and examined associations with child characteristics, maternal demographic and reproductive history characteristics, and maternal pre-pregnancy and periconceptional exposures. Our study of 101 cases is one of the largest to date to examine risk factors for CDs. The clinical classification of CDs into potentially more homogeneous groupings of CE and PC (inclusive of URSMS), including presence of other associated and atypical defects, provides additional insight into pathogenesis for CDs.

We observed that CDs grouped as CE or PC had similar and overlapping kidney, urinary, GI, and skeletal/ spinal defects. The most frequently associated defects with both multiple CE and PC were congenital heart defects. CE has overlapping findings with LBWC, including its association with limb deficiency defects, whereas PC more often had overlapping

findings with VACTERL association. This overlap between CE, PC, LBWC, and VACTERL association was reported previously and may suggest that these conditions represent a spectrum and share a common pathogenetic mechanism [Bohring, 2002; Curry et al., 2006; Heyroth-Griffis, et al., 2007; Keppler-Noreuil, et al., 2007; Feldkamp et al., 2011]; however, CE and PC do have distinguishing characteristics. In particular, isolated CE occurred more frequently compared to isolated PC, which was more likely to have other multiple, unassociated defects. Kubota et al. [2017] and Tennant et al. [2014] also observed in their descriptive population-based study that most cases of PC had additional structural birth defects, including renal (in one-half of cases), digestive, system, cardiovascular, or limb anomalies (in one-quarter of cases).

For all CDs, we observed an excess of females, attributed to PC cases. There were almost equal counts of females (22) and males (21) with CE, whereas there were 49 females and 4 males included under the PC designation. These results are similar to other studies of CE and PC [Martinez-Frias et al., 2001; Caton et al., 2007; Feldkamp et al., 2011; Kubota, 2017]. In this study, PC was considered inclusive of URSMS, as have other researchers studying these malformations [Tennant et al., 2014; Cuschieri et al., 2001; Wheeler et al., 2001]. In addition, the NBDPS study used the ICD-9 Clinical Modification coding scheme, and there is only a code for PC (not URSMS); however, the cloacal defects described under this code include the URSMS. Urorectal septum malformation sequence may occur in both males and females as documented by Wheeler et al. [2001]; when it occurs in females, these malformations are often referred to as persistent cloaca [Peña, 2016].

We observed that preterm birth was positively associated with CE and PC compared to controls, and higher among CE cases compared to cases with PC. Associations between preterm birth and CE were described in two previous studies [Caton et al., 2007; Martinez-Frias et al., 2001]. We also observed that plurality was significantly associated with CE, but not PC. Among the different hypotheses of CE pathogenesis, the association with plurality may support two particular hypotheses. One hypothesis being that both CE and twinning may be manifestations of the same early disturbance of morphogenesis, occurring as early as blastogenesis [Schinzel et al., 1979; McLaughlin et al., 1984]. The second hypothesis being that partial or complete duplication of the organizing center within a single embryonic disc may increase the risk of mesodermal insufficiency, accounting for failure of cloacal membrane development leading to exstrophy [Siebert et al, 2005].

Sadler and Feldkamp [2008] also proposed that disruption of the embryonic disc and failure of migration of the lateral body wall folds to meet at the midline could lead to ventral body wall defects. During later stages of gastrulation, the caudal eminence functions as a developmental field that is modulated by homeobox genes and a variety of other factors. Histopathologic studies in human embryos also support that CE is likely the result of a very early defect of insufficient cellular proliferation or deposition involving the caudal eminence [Hartwig et al., 1991; Nievelstein et al., 1998; Van der Putte et al., 2008; Feldkamp et al., 2011].

Our analysis of selected maternal characteristics and exposures was based in part upon previous anecdotal reports and known risk factors for component or related birth defects

(e.g. caudal dysgenesis, neural tube defects, sacral agenesis with maternal diabetes) [Yazdy et al., 2010; Dheen et al., 2009; Zhu et al., 2009; Chappell et al., 2009], and folate deficiency [Czeizel and Dudas, 1992]. The positive associations observed for use of any fertility medication or an ART procedure with any CD, CE, and PC were statistically significant in crude and adjusted analyses. An increased risk for anorectal malformations and exstrophy-epispadias complex in children born after ART with both in-vitro fertilization and intracystoplasmic sperm injection was reported in two German case-control studies [Zwink et al., 2012; Zwink et al., 2013]. In an earlier analysis using NBDPS data through 2005, Reefhuis et al. [2011] reported a significant positive association for CE with use of clomiphene citrate (aOR = 5.4; 95% CI = 1.6–19.3).

Significant positive associations observed in crude analysis for reports of maternal obesity (with any CD) and any x-ray (with any CD and CE) had no covariables meet the criteria for inclusion in an adjusted model. Risk of birth defects (including defects of the heart, central nervous system defects, limbs, urinary tract, and genital systems) in offspring of mothers who were in overweight and obesity categories were observed to be higher than background risk of major malformations in the general population [Persson et al., 2017; Tang et al., 2015; Stothard et al., 2009]. Our study supports these findings, and adds CDs as specific anorectal and genital defects that show a positive association with maternal obesity. Further, we observed associations with any CD and CE with any maternal x-ray exposure. Exposure to x-rays as a risk factor for any CD specifically has not been previously reported. The risks of teratogenic effects from x-rays (ionizing radiation) vary based upon the radiation dose and the stage of development of the embryo/fetus, with the greatest susceptibility during organogenesis (two to seven weeks after conception) and in the early fetal period (eight to 15 weeks after conception) [Williams and Fletcher, 2010; Streffer et al., 2003]. These are also the critical periods when development from the cloaca to the urinary, genital, and lower gastrointestinal tract are occurring. These associations provide some of the first insights into differing risk for CE and PC with several maternal exposures. Additional significant positive associations for use of progesterone (any CD) and use of folate antagonist medications (any CD and PC) observed in crude analysis either did not persist in adjusted analysis (progesterone) or had too few exposed case mothers to conduct adjusted analysis (folate antagonist medications).

One of the strengths of our study is that it is one of the largest to date examining risk factors for CDs. Previous studies had smaller numbers of cases of CE, and either did not have a case-control design or did not separately analyze cases with CE (cases of CE were combined with BE and PC cases). Another strength of our study was that clinical information was abstracted from medical records and reviewed by clinical geneticists to ensure cases met the criteria for inclusion (and had confirmation of the diagnosis). Additionally, the extensive interview data collected from mothers of children in the NBDPS allowed for examining associations between a wide spectrum of possible characteristics and exposures and CE and PC.

Examination of a large number of characteristics and exposures was also a potential limitation. Because of the rather limited literature on risk factors for CDs, our study was intended to be a hypothesis-generating study, so we did not adjust for multiple comparisons.

Relatedly, because of the rather modest number of exposed cases for some risk factors, we examined each risk factor independently rather than as combinations of risk factors. Our analyses were also based on retrospective self-reports of exposures, which may have introduced recall bias between case and control mothers. Additionally, nearly one-third of mothers contacted declined to be interviewed raising concerns about the generalizability of our findings, and bias may have been introduced due to unmeasured differences between maternal participants and non-participants; however, control mothers participating in the NBDPS have been reported to be generally representative of the underlying population from which they were selected [Cogswell et al., 2009].

The involvement of structures in the caudal developmental field and the likely differences in embryologic timing of these CDs suggest there may be disruption of spatiotemporal gene expression in separate genes in the same pathway. There are other groups of conditions with similar overlapping features caused by mutations in signaling pathway genes, for example in the disorders of the RAS-MAPK (Rasopathies) and the PI3K-AKT pathways. We hypothesize that CE with its features, including its sporadic occurrence, predominantly isolated presentation, and the caudal distribution of its composite defects, is caused in large part by an early somatic mutation. Potential candidate genes may include one of the homeobox genes, such as *HLXb9*, *p63*, or *SHH-WNT-PTC1-GL1* signaling genes. These genes have not been identified to date, because previous genetic studies used blood specimens to examine germline mutations. The expression of these somatic mutations also may be modified by other mutations or environmental risk factors. Based upon this hypothesis, our future studies will include evaluating affected tissue from individuals with CE for somatic mosaicism.

In summary, our clinical and risk factor analysis identified statistically significant positive associations with reported maternal use of any fertility medication or an ART procedure, pre-pregnancy obesity, and periconceptional exposure to x-rays. We observed that although there is overlap in the clinical and epidemiologic findings of CE and PC, there are distinct differences, which suggest that these conditions may have different etiologies. Both our clinical findings and positive associations with maternal exposures suggest possible hypotheses for etiology and pathogenesis of CDs. Further investigations of the role of genetic, including somatic mutations, and potential interacting environmental risk factors for CDs, and in particular CE, are needed to understand the underlying cause(s) of these defects.

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Table I

Clinical findings for cloacal defects by subtype, National Birth Defects Prevention Study, 1997–2011.

Cloacal Exstrophy (N=47)				Persistent Cloaca[a] (N=54)			
Isolated (N=33)		Multiple (N=14)		Isolated (N=26)		Multiple (N=28)[b]	
Defect	**N (%)**	**Defect**	**N (%)**	**Defect**	**N (%)**	**Defect**	**N (%)**
Limb Body Wall Complex (1 Short Umbilical Cord)	2 (6.0)	Choanal Atresia	1 (7.1)	Limb Body Wall Complex (Possible)	1 (2.6)	Central Nervous System Defects	4 (14.2)
		Congenital Diaphragmatic Hernia	1 (7.1)			Congenital Heart Defects	17 (60.7)
		Congenital Heart Defects	7 (50.0)			Esophageal Atresia/Stenosis	3 (10.7)
		Hydrocephalus, No Neural Tube Defect	1 (7.1)			Laterality Defects	3 (10.7)
		Limb Defect (Unilateral Tibial Aplasia)	4 (28.6)			Radial Defects	1 (3.6)
						VACTERL Association (Possible)	7 (25.0)

[a] Includes urorectal septum malformation sequence.

[b] A case may have more than one defect or defect group listed.

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Table II

Comparison of child and maternal characteristics between controls and any cloacal defect or subtype, and between subtypes, National Birth Defects Prevention Study, 1997–2011.

						Cloacal Defect Subtypes						
	Controls		Any Cloacal Defect			Cloacal Exstrophy			Persistent Cloaca[b]			Cloacal Exstrophy vs. Persistent Cloaca
Characteristic	**N[a]**	**%**	**N[a]**	**%**	***p***	**N[a]**	**%**	***p***	**N[a]**	**%**	***p***	***p***
Total	11829		101			47			54			
Child												
Sex					**<0.001**			0.779			**<0.001**	**<0.001**
Male	6024	51.0	25	26.0		21	48.8		4	7.6		
Female	5793	49.0	71	74.0		22	51.2		49	92.5		
Ambiguous	0		3			2			1			
Missing	12		2			2			0			
Gestational Age (weeks)					**<0.001**			**<0.001**[c]			**<0.001**	**0.005**
Preterm (<37)	1100	9.3	65	64.4		37	78.7		28	51.9		
Term (37–45)	10727	90.7	36	35.6		10	21.3		26	48.2		
Missing	2		0			0			0			
Plurality					**<0.001**[c]			**<0.001**[c]			0.675[b]	**0.013**
Multiple	351	3.0	11	10.9		9	19.2		2	3.7		
Singleton	11477	97.0	90	89.1		38	80.9		52	96.3		
Missing	1		0			0			0			
Maternal												
Age at Delivery (years)					0.205			0.272			0.497	0.685
<20	1177	10.0	15	14.9		8	17.0		7	13.0		
20–34	8988	76.0	75	74.3		33	70.2		42	77.8		
≥35	1664	14.1	11	10.9		6	12.8		5	9.3		
Missing	0		0			0			0			
Race and Ethnicity					0.857			0.759			0.346	0.331[c]
Non-Hispanic White	6836	57.8	57	56.4		25	53.2		32	59.3		
Non-Hispanic Black	1308	11.1	13	12.9		6	12.8		7	13.0		

Characteristic	Controls		Any Cloacal Defect			Cloacal Defect Subtypes						
						Cloacal Exstrophy			Persistent Cloaca[b]			Cloacal Exstrophy vs. Persistent Cloaca
	N[a]	%	N[a]	%	*p*	N[a]	%	*p*	N[a]	%	*p*	*p*
Hispanic	2908	24.6	23	22.8		14	29.8		9	16.7		
Other	770	6.5	8	7.9		2	4.3		6	11.1		
Missing	7		0			0			0			
Education at Delivery (years)					0.407			0.052			0.694	0.134
<12	1905	16.6	21	21.2		14	29.8		7	13.5		
12	2725	23.7	20	20.2		9	19.2		11	21.2		
≥13	6854	59.7	58	58.6		24	51.1		34	65.4		
Missing	345		2			0			2			
Gravidity					0.298			0.889			0.239	0.720
First Pregnancy	3471	29.5	36	35.6		15	31.9		21	38.9		
Second Pregnancy	3347	28.4	23	22.8		12	25.5		11	20.4		
Third or Higher Pregnancy	4960	42.1	42	41.6		20	42.6		22	40.7		
Missing	51		0			0			0			
Study Site					0.679			0.884			0.307	0.314[c]
Arkansas	1471	12.4	8	7.9		5	10.6		3	5.6		
California	1263	10.7	15	14.9		6	12.8		9	16.7		
Iowa	1300	11.0	13	12.9		7	14.9		6	11.1		
Massachusetts	1402	11.9	11	10.9		5	10.6		6	11.1		
New Jersey	578	4.9	6	5.9		3	6.4		3	5.6		
New York	989	8.4	9	8.9		3	6.4		6	11.1		
Texas	1416	12.0	8	7.9		7	14.9		1	1.9		
CDC	1267	10.7	10	9.9		2	4.3		8	14.8		
North Carolina	1016	8.6	8	7.9		3	6.4		5	9.3		
Utah	1127	9.5	13	12.9		6	12.8		7	13.0		
Missing	0		0			0			0			
Previous miscarriage					0.623			0.354			0.124	0.093
Yes	2673	22.7	25	24.8		8	17.0		17	31.5		
No	9105	77.3	76	75.3		39	83.0		37	68.5		

						Cloacal Defect Subtypes						
	Controls		Any Cloacal Defect			Cloacal Exstrophy			Persistent Cloaca[b]			Cloacal Exstrophy vs. Persistent Cloaca
Characteristic	N[a]	%	N[a]	%	*p*	N[a]	%	*p*	N[a]	%	*p*	*p*
Missing	51		0			0			0			
Planned Pregnancy					0.956			0.770			0.896	0.741[c]
Yes	7096	60.5	61	60.4		30	63.8		31	57.4		
No	3798	32.4	32	31.7		13	27.7		19	35.2		
Did Not Care	843	7.2	8	7.9		4	8.5		4	7.4		
Missing	92		0			0			0			

Numbers vary because of incomplete or missing data. Because of rounding, percentages might not total 100.

[a] Missing values not included in chi-square or Fisher's exact test.

[b] Includes urorectal septum malformation sequence.

[c] Fisher's exact test.

Table III

Covariables included in adjusted models of maternal pre-pregnancy and periconceptional exposures between controls and any cloacal defect or subtype, National Birth Defects Prevention Study, 1997–2011.

		Cloacal Defect Subtypes	
Exposure[a]	**Any Cloacal Defect**	**Cloacal Exstrophy**	**Persistent Cloaca**[b]
Fertility Medication or ART Procedure	child plurality; maternal age at delivery	child sex and plurality; maternal age at delivery, race/ethnicity, and education at delivery	child sex; maternal age at delivery
Chorionic Villus Sampling	NC	NC	NC
Pre-Pregnancy BMI (kg/m^2)	none	none	none
Hypertension, Lifetime	none	child sex	none
Pre-Pregnancy Caffeine Consumption (mg/day)	child sex; maternal study site	child sex	child sex; maternal study site
Infection Due to UTI or PID	none	child sex	none
Fever	child sex	child sex	child sex
Any X-ray	none	none	NC
Progesterone	child plurality; maternal age at delivery	NC	NC
Folic Acid Supplemented Multivitamins	none	maternal education at delivery	maternal education at delivery
Vasoactive Medications	none	none	none
Folate Antagonist Medications	NC	NC	NC
Cigarette Smoking	none	none	maternal education at delivery and study site
Alcohol Consumption	none	maternal education at delivery	none
Illicit Drug Use	none	NC	NC

ART, Assisted Reproductive Technology; BMI, Body Mass Index; NC, not calculated (<5 exposed case mothers); PID, pelvic inflammatory disease; UTI, urinary tract infection.

[a] Three maternal exposures – pre-pregnancy diabetes (type I or II), periconceptional use of vitamin A supplements, and periconceptional use of retinoic acid medications – had no exposed case mothers.

[b] Includes urorectal septum malformation sequence.

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Table IV

Crude odds ratios of maternal pre-pregnancy and periconceptional exposures between controls and any cloacal defect or subtype, National Birth Defects Prevention Study, 1997–2011.

						Cloacal Defect Subtypes					
	Controls		Any Cloacal Defect			Cloacal Exstrophy			Persistent Cloaca[a]		
Exposure	**N**	**%**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**
Total	11829		101			47			54		
Fertility Medication or ART Procedure											
Yes	534	4.5	15	14.9	**3.7 (2.1, 6.4)**	7	14.9	**3.7 (1.6, 8.3)**	8	14.8	**3.7 (1.7, 7.8)**
No	11227	95.5	86	85.2	Referent	40	85.1	Referent	46	85.2	Referent
Missing	68		0			0			0		
Chorionic Villus Sampling											
Yes	463	4.0	3	3.0	0.7 (0.2, 2.3)[b]	0	0.0	0.4 (0.0, 1.6)[b]	3	5.7	1.4 (0.3, 4.5)[b]
No	11143	96.0	97	97.0	Referent	47	100	Referent	50	94.3	Referent
Missing	223		1			0			1		
Pre-Pregnancy BMI (kg/m^2)											
Underweight (<18.5)	599	5.3	7	7.5	1.7 (0.8, 3.9)	4	9.1	2.0 (0.5, 6.1)[b]	3	6.1	1.4 (0.3, 4.8)[b]
Normal (18.5–24.9)	6045	53.6	41	44.1	Referent	20	45.45	Referent	21	42.9	Referent
Overweight (25.0–29.9)	2557	22.7	21	22.6	1.2 (0.7, 2.1)	10	22.7	1.2 (0.5, 2.7)[b]	11	22.5	1.2 (0.5, 2.7)[b]
Obese (≥30.0)	2074	18.4	24	25.8	**1.7 (1.0, 2.8)**	10	22.7	1.5 (0.6, 3.3)[b]	14	28.6	1.9 (0.9, 4.0)[b]
Missing	554		8			3			5		
Hypertension, Lifetime											
Yes	1609	13.7	18	17.8	1.4 (0.8, 2.3)	8	17.0	1.3 (0.6, 2.8)	10	18.5	1.4 (0.7, 2.9)
No	10145	86.3	83	82.2	Referent	39	83.0	Referent	44	81.5	Referent
Missing	75		0			0			0		
Pre-Pregnancy Caffeine Consumption (mg/day)											
≤10	4875	42.3	41	41.4	Referent	21	44.7	Referent	20	38.5	Referent
>10 and <100	2686	23.3	20	20.2	0.9 (0.5, 1.5)	10	21.3	0.9 (0.4, 1.8)	10	19.2	0.9 (0.4, 2.0)[b]
≥100 and <200	2040	17.7	19	19.2	1.1 (0.6, 1.9)	6	12.8	0.7 (0.3, 1.7)	13	25.0	1.6 (0.7, 3.3)[b]

	Controls		Any Cloacal Defect			Cloacal Defect Subtypes					
						Cloacal Exstrophy			Persistent Cloaca[a]		
Exposure	**N**	**%**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**
≥200 and <300	1098	9.5	10	10.1	1.1 (0.5, 2.2)	5	10.6	1.1 (0.4, 2.8)	5	9.6	1.1 (0.3, 3.1)[b]
≥300	829	7.2	9	9.1	1.3 (0.6, 2.7)	5	10.6	1.4 (0.5, 3.7)	4	7.7	1.2 (0.3, 3.5)[b]
Missing	301		2			0			2		
Infection Due to UTI or PID											
Yes	837	7.2	10	10.1	1.4 (0.7, 2.8)	5	10.9	1.6 (0.6, 4.0)	5	9.4	1.3 (0.5, 3.4)
No	10730	92.8	89	89.9	Referent	41	89.1	Referent	48	90.6	Referent
Missing	262		2			1			1		
Fever											
Yes	1163	9.8	10	9.9	1.0 (0.5, 1.9)	5	10.6	1.1 (0.4, 2.8)	5	9.3	0.9 (0.4, 2.4)
No	10666	90.2	91	90.1	Referent	42	89.4	Referent	49	90.7	Referent
Missing	0		0			0			0		
Any X-ray											
Yes	487	4.2	9	9.2	**2.3 (1.2, 4.6)**	8	17.0	**4.7 (2.2, 10.2)**	1	2.0	0.5 (0.0, 2.7)[b]
No	11198	95.8	89	90.8	Referent	39	83.0	Referent	50	98.0	Referent
Missing	144		3			0			3		
Progesterone											
Yes	310	2.6	6	6.0	**2.4 (1.0, 5.5)**	2	4.3	1.7 (0.2, 6.4)[b]	4	7.6	3.0 (0.8, 8.3)[b]
No	11516	97.4	94	94.0	Referent	45	95.7	Referent	49	92.5	Referent
Missing	3		1			0			1		
Folic Acid Supplemented Multivitamins											
Yes	10024	85.9	81	81.0	0.7 (0.4, 1.2)	40	85.1	0.9 (0.4, 2.1)	41	77.4	0.6 (0.3, 1.1)
No	1640	14.1	19	19.0	Referent	7	14.9	Referent	12	22.6	Referent
Missing	165		1			0			1		
Vasoactive Medications											
Yes	3994	34.4	35	35.7	1.1 (0.7, 1.6)	14	30.4	0.8 (0.4, 1.6)	21	40.4	1.3 (0.7, 2.3)
No	7622	65.6	63	64.3	Referent	32	69.6	Referent	31	59.6	Referent
Missing	213		3			1			2		
Folate Antagonist Medications											

	Controls		Any Cloacal Defect			Cloacal Defect Subtypes					
						Cloacal Exstrophy			Persistent Cloaca[a]		
Exposure	**N**	**%**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**	**N**	**%**	**cOR (95% CI)**
Yes	110	0.9	4	4.0	**4.4 (1.2, 11.9)**[b]	1	2.1	2.3 (0.1, 13.8)[b]	3	5.6	**6.3 (1.2, 19.8)**[b]
No	11707	99.1	97	96.0	Referent	46	97.9	Referent	51	94.4	Referent
Missing	12		0			0			0		
Cigarette Smoking											
None	7997	69.7	59	64.8	Referent	30	68.2	Referent	29	61.7	Referent
Active Smoking Only	871	7.6	9	9.9	1.4 (0.7, 2.8)	4	9.1	1.2 (0.3, 3.5)[b]	5	10.6	1.6 (0.6, 4.1)
Passive Smoking Only	1425	12.4	12	13.2	1.1 (0.6, 2.1)	6	13.6	1.1 (0.4, 2.7)[b]	6	12.8	1.2 (0.5, 2.8)
Active and Passive Smoking	1188	10.4	11	12.1	1.3 (0.7, 2.4)	4	9.1	0.9 (0.2, 2.6)[b]	7	14.9	1.6 (0.7, 3.7)
Missing	348		10			3			7		
Alcohol Consumption											
None	7209	63.3	61	64.9	Referent	29	64.4	Referent	32	65.3	Referent
Yes, No Binging	2780	24.4	25	26.6	1.1 (0.7, 1.7)	12	26.7	1.1 (0.5, 2.2)[b]	13	26.5	1.1 (0.5, 2.1)
Yes, Binging	1396	12.3	8	8.5	0.7 (0.3, 1.4)	4	8.9	0.7 (0.2, 2.0)[b]	4	8.2	0.6 (0.2, 1.8)
Missing	444		7			2			5		
Illicit Drug Use											
Yes	501	4.4	5	5.1	1.2 (0.5, 2.9)	2	4.3	1.0 (0.1, 3.8)[b]	3	5.9	1.4 (0.3, 4.3)[b]
No	11005	95.7	93	94.9	Referent	45	95.7	Referent	48	94.1	Referent
Missing	323		3			0			3		

ART, Assisted Reproductive Technology; BMI, Body Mass Index; cOR, crude odds ratio; CI, confidence interval; NC, not calculated (<5 exposed case mothers); PID, pelvic inflammatory disease; UTI, urinary tract infection.

Numbers vary because of incomplete or missing data. Because of rounding, percentages might not total 100.

[a] Includes urorectal septum malformation sequence.

[b] Exact CI