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Use of clomiphene citrate and birth defects, National Birth Defects Prevention Study, 1997–2005

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BACKGROUND: Clomiphene citrate (CC) is the first line drug for subfertility treatment. Studies assessing the association between CC and birth defects have been inconclusive.

METHODS: We used data from the National Birth Defects Prevention Study, a population-based, multi-site case–control study of major birth defects. Women from 10 US regions with deliveries affected by at least one of >30 birth defects (cases) and mothers of live born infants without a major birth defect (controls) who delivered October 1997–December 2005 were interviewed. The exposure of interest was reported CC use in the period from 2 months before conception through the first month of pregnancy. Women who conceived using assisted reproductive technology were excluded. Thirty-six birth defect categories with at least three exposed cases were studied. Multiple logistic regression was used to control for potential confounders.

RESULTS: CC use was reported by 1.4% of control mothers (94/6500). Among 36 case-groups assessed, increased adjusted odds ratios (aOR) were found [all: aOR, 95% confidence interval (CI)] for anencephaly (2.3, 1.1–4.7), Dandy–Walker malformation (4.4, 1.7–11.6), septal heart defects (1.6, 1.1–2.2), muscular ventricular septal defect (4.9, 1.4–16.8), coarctation of aorta (1.8, 1.1–3.0), esophageal atresia (2.3, 1.3–4.0), cloacal exstrophy (5.4, 1.6–19.3), craniosynostosis (1.9, 1.2–3.0) and omphalocele (2.2, 1.1–4.5).

CONCLUSIONS: Several associations between CC use and birth defects were observed. However, because of the small number of cases, inconsistency of some findings with previous reports, and the fact that we cannot assess the CC effect separately from that of the subfertility, these associations should be interpreted cautiously.

Key words: clomiphene citrate / ovulation stimulation / birth defects / congenital malformations

Introduction

According to data from the 2002 National Survey of Family Growth, 11.9% of US women aged 15–44 years reported ever using any infertility treatment (Chandra *et al.*, 2005). In this 2002 survey, 3.8% of women indicated they ever used ovulation drugs, which is a 27% increase since the 1995 survey (Abma *et al.*, 1997) when 3% of women indicated ever using ovulation stimulating drugs. Clomiphene citrate (CC) is a non-steroidal ovulation-inducing drug that has been used in humans for more than 40 years (Anonymous, 1968). In a recent study using managed care data, 2.0% of randomly selected singleton term infants were conceived using CC (Wu *et al.*, 2006). A recent descriptive analysis of fertility treatment from the National Birth Defects Prevention Study (NBDPS) for birth years 1997–2004 reported that 1.6% of control-mothers (mothers of live born infants without birth defects) used CC without assisted reproduction technologies (ART) at any time from 2 months before to the end of the current pregnancy (Duwe *et al.*, 2010). Given the frequency of use of CC, it is important to understand any possible risks associated with its use.

Two types of birth defects that have been most commonly reported to be associated with CC exposure in previous studies are neural tube defects (NTDs) and hypospadias; however, results regarding the association between CC and these birth defects have been inconsistent (Greenland and Ackerman, 1995; Sorensen *et al.*, 2005; Meijer *et al.*, 2006; Wu *et al.*, 2006). Additionally, we previously observed an association between CC and craniosynostosis in a case–control study conducted from 1993 to 1997, but were not able to control for potential confounders owing to sparse data (Reefhuis *et al.*, 2003).

We used data from the NBDPS, a multi-site population-based case–control study of major birth defects of unknown etiology, to study the association between CC and birth defects. In this analysis, we sought to replicate the previous findings that CC is associated with NTDs, hypospadias or craniosynostosis. In addition, we assessed the association between CC and several other birth defects.

Materials and Methods

The NBDPS is an ongoing multi-site case–control study of more than 30 different major birth defects that started collecting data with births on or after 1 October 1997 (Yoon *et al.*, 2001). The primary objective of the NBDPS is to identify environmental and genetic risk factors for birth defects; therefore, case-infants with recognized or strongly suspected single-gene or chromosomal conditions were excluded from the study. Case-infants were identified using existing birth defects surveillance systems in 10 US states (AR, CA, GA, IA, MA, NJ, NY, NC, TX and UT). Information on birth defects abstracted from hospital records was reviewed by a clinical geneticist at each study site to ensure that the case definition was met. Details of the clinical methods of the study have been published elsewhere (Rasmussen *et al.*, 2003). Control-infants were a random sample of live born infants without any major birth defects that were selected from the same geographical area and time period either from birth certificates (using the number of births each month for the previous year to select a proportionate number of controls) or hospital birth records (weighted by the annual number of births in each hospital). Only one child from each family is included in the study. In case of twins where both are eligible for the study, only the first-born twin is included.

Mothers of case- and control-infants participated in a computer-assisted telephone interview, which included questions on pregnancy history, lifestyle, fertility treatments, occupation and demographic factors, in either English or Spanish. Case- and control-infants for this analysis were limited to births on or after 1 October 1997, and with an estimated date of delivery on or before 31 December 2005. The response rate for the interview was 69% for case-mothers and 66% for control-mothers. Case- and control-mothers who reported a diagnosis of type 1 or type 2 diabetes before pregnancy were excluded because of the strong association between pregestational diabetes and major birth defects (Correa *et al.*, 2008). For some defect categories not all controls were included; for example, for the hypospadias analyses only male control infants were included.

Exposure

Exposure to CC was determined through the interview question 'In the two months before you became pregnant . . . did you take any medications to help you become pregnant?' The name and start and stop month of each fertility medication were recorded.

For this analysis, use of CC was defined as any reported use of CC in the period from 2 months before through the first month of pregnancy. Women who used CC in combination with intrauterine insemination (IUI) were included in this group. Women who used CC in combination with other fertility drugs, or in combination with ART including IVF or ICSI were excluded from these analyses. Only women who reported that neither they nor the father of the baby took any medications or had any procedures to help her to become pregnant during this time period were considered unexposed and served as a comparison group.

Statistical analysis

We included defect categories that had at least 150 cases including at least three exposed cases (to avoid assessing case-groups with insufficient statistical power), and also smaller categories with at least three exposed cases (to identify rare defects strongly associated with the exposure). Univariate analyses were used to calculate crude odds ratios (OR) for each exposure-outcome combination; OR were considered statistically significant if the *P*-value was smaller than 0.05. If the expected number in any of the cells was less than five, Fisher's exact test was used to estimate the confidence interval (CI). Multiple logistic regression models were computed to calculate adjusted odds ratios (aOR). A priori selected confounders included in the multivariable analyses were maternal age (continuous), maternal race (white, other), parity (no previous live births, at least one previous live birth), previous miscarriages (0, $\geq$1), BMI ($<$30, $\geq$30), education ($\leq$12 years, $>$12 years), maternal smoking or alcohol use from 1 month before pregnancy through the end of the first trimester (any, none), and use of folic acid or multivitamin supplements in the month before pregnancy or first month of pregnancy (yes/no). We considered including study site as a confounder, but the data did not suggest an effect and much precision would have been lost by adding a 9-level variable to the model. We did not include twinning as a potential confounder because it is likely in the causal pathway between CC exposure and birth defects.

Subgroup analyses were performed including only singleton pregnancies, and only pregnancies that the mother self-reported as intended (Dott *et al.*, 2010). Separate analyses were conducted including only isolated cases (no other major unrelated birth defects), categorizing maternal age instead of using maternal age as a continuous variable, and excluding pregnancies conceived via IUI. Both second (urethral meatus on the shaft) and third (urethral meatus on the scrotum or perineum) degree hypospadias are included in the NBDPS and they usually are analyzed as a group. Because of a paper by Meijer *et al.* (2006) that reported an effect of CC for penoscrotal hypospadias, but not for mild or moderate hypospadias we also assessed second and third degree hypospadias separately.

Study population

Overall, 19 059 mothers of children with a birth defect (case-mothers) and 6807 mothers of children without birth defects (control-mothers) with delivery dates between 1 October 1997 and 31 December 2005 participated in the interview (Fig. 1). No fertility treatment (unexposed) was reported by 23 667 and CC use in the period from 2 months before to the first month of pregnancy was reported by 440. There was no difference in the number of women who reported using CC among those that did their interview within 9 months after the estimated date of delivery and those that were interviewed later. There were 35 categories of birth defects that had at least 150 cases, 4 of these had less than 3 exposed cases (total anomalous pulmonary venous return, single ventricle, gastroschisis and longitudinal limb defects) and were not studied. There were five additional defect categories that had $<$150 total cases, but more than 3 exposed cases that were included. In total, we assessed 36 categories of birth defects.

Results

Among control-mothers, women who reported using CC were significantly more likely to give birth to twins or higher plurality, more often 25 years or older, non-Hispanic white, had no previous live births, more highly educated, more often obese, more likely to take a multivitamin containing folic acid, and reported more previous miscarriages (Table I) compared with the unexposed mothers.

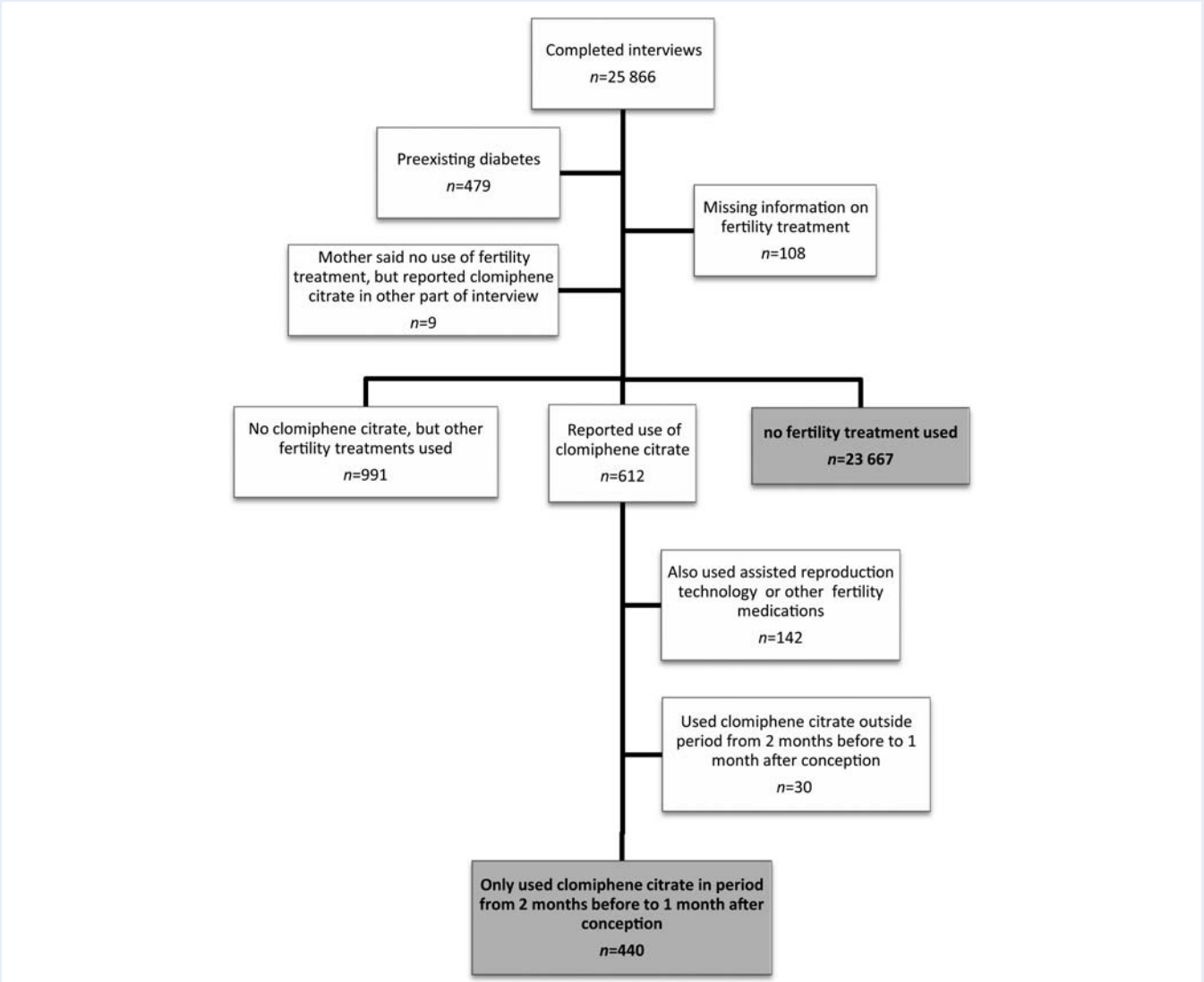

Figure 1 Exclusions for cases and controls in the analyses of CC and birth defects. National Birth Defects Prevention Study 1997–2005.

We assessed crude and aOR for 36 defect categories (Table II). We saw crude OR greater than 1.8 for all defect categories previously reported in the literature to be associated with CC use (anencephaly, hypospadias, craniosynostosis). After adjusting for the selected confounders, we no longer observed a significant association for hypospadias. For anencephaly and craniosynostosis the aOR were significant (aOR 2.3, 95% CI 1.1–4.7 and aOR 1.9, 95% CI 1.2–3.0, respectively). Other defects that were associated with CC use after adjustment for potential confounders were Dandy Walker malformation (aOR 4.4, 95% CI 1.7–11.6), septal heart defects (aOR 1.6, 95% CI 1.1–2.2), muscular ventricular septal heart defects (aOR 4.9, 95% 1.4–16.8), coarctation of the aorta (aOR 1.8, 95% CI 1.1–3.0), esophageal atresia (aOR 2.3, 95% CI 1.3–4.0), cloacal exstrophy (aOR 5.4, 95% CI 1.6–19.3) and omphalocele (aOR 2.2, 95% CI 1.1–4.5). When we limited the data to singleton births, we observed significant associations for Dandy–Walker malformation, muscular ventricular septal defect (VSD), esophageal atresia and cloacal exstrophy. In analyses limited to pregnancies that the mother indicated were intended, most estimates were increased, but not substantially (data not shown). In analyses limited to isolated defects we observed slightly decreased OR, with the exception of muscular VSD and choanal atresia for which OR were increased (aOR 5.7, 95% CI 1.7–19.6 and aOR 4.3, 95% CI 1.2–15.2, respectively). The effect estimates were similar when we used a 3-level variable for maternal age instead of a continuous variable or when we excluded pregnancies that used IUI in addition to CC.

In our assessment of second and third degree hypospadias, the crude ORs were greater than two and significant (OR were 2.1 and 2.5, respectively); however, both ORs decreased (1.3 and 1.2, respectively) after adjustment for confounders and were no longer significant. We assessed the individual influence of maternal age, race and parity on the association between CC and second- and third-degree hypospadias combined: none of the factors was solely responsible for the decrease in the odds ratio. Including these factors in groups

Table I Characteristics of control mothers with an unassisted conception, or mothers with reported use of CC, National Birth Defects Prevention Study, 1997–2005.

	Unassisted conception (n = 6406)	CC (n = 94)[a]
Multiple births		
Singletons	6270 (97.9%)	82 (87.2%)
Twins	128 (2.0%)	11 (11.7%)
Triplets/quadruplets	3 (0.1%)	1 (1.1%)
Maternal age		
<25 years	2240 (35.0%)	6 (6.4%)
25–29 years	1720 (26.8%)	27 (28.7%)
30–34 years	1608 (25.1%)	40 (42.6%)
35–39 years	721 (11.3%)	16 (17.0%)
40+ years	117 (1.8%)	5 (5.3%)
Maternal race/ethnicity		
Non-Hispanic white	3717 (58.3%)	88 (93.6%)
Non-Hispanic black	747 (11.7%)	3 (3.2%)
Hispanic	1465 (23.0%)	1 (1.1%)
Other	449 (7.0%)	2 (2.1%)
Previous live births		
None	2515 (39.3%)	53 (56.4%)
One	2149 (33.6%)	29 (30.9%)
Two or more	1741 (27.2%)	12 (12.8%)
Previous miscarriages		
None	5020 (78.4%)	62 (66.0%)
One	1054 (16.5%)	21 (22.3%)
Two or more	331 (5.2%)	11 (11.7%)
Maternal education		
<12 years	1110 (17.5%)	1 (1.1%)
12 years	1597 (25.2%)	9 (9.6%)
>12 years	3618 (57.2%)	84 (89.3%)
BMI		
<18.5 kg/m^2	349 (5.7%)	3 (3.2%)
18.5–24.9 kg/m^2	3450 (56.2%)	42 (4.7%)
25–9.9 kg/m^2	1373 (22.3%)	22 (23.4%)
30+ kg/m^2	972 (15.8%)	27 (28.7%)
Smoking from one month before pregnancy through the first trimester	1232 (19.4%)	11 (11.7%)
Alcohol use from one month before pregnancy through the first trimester	2329 (36.9%)	30 (31.9%)
Folic acid-containing multivitamin use from one month before pregnancy through the first month of pregnancy	3136 (49.1%)	85 (90.4%)
Study site[b]		
Arkansas	802 (12.5%)	16 (17.0%)
California	831 (13.0%)	1 (1.1%)
Georgia	696 (10.9%)	7 (7.4%)
Iowa	705 (11.0%)	20 (21.3%)
Massachusetts	775 (12.1%)	15 (16.0%)
New Jersey	546 (8.5%)	4 (4.3%)
New York	569 (8.9%)	6 (6.4%)
North Carolina	384 (6.0%)	7 (7.4%)
Texas	751 (11.7%)	7 (7.4%)
Utah	347 (5.4%)	11 (11.7%)

Subjects with pre-existing diabetes type 1 or 2 were excluded.
Totals do not always equal 6406 because of missing information.
[a]Women who used ART or other fertility drugs were not included.
[b]Data collection is state-wide in AR, IA and UT. All other sites include a defined geographic region of the state with between 35 000 and 75 000 births per year.

of two also did not identify a specific subset of confounders that was responsible. Instead, it appears that the combined contributions of all three confounders caused the attenuation of the OR from 2.3 to 1.5.

Excluding centers with surveillance systems that do not routinely ascertain pregnancy terminations (MA, NJ and NY) lowered the observed association between CC and anencephaly (aOR 1.8, 95% CI 0.8–4.0), did not change the estimate for spina bifida, and increased the observed association with encephalocele (aOR 3.7, 95% CI 1.3–11.4).

Discussion

In this multi-site, population-based case–control study, we identified associations between use of CC and anencephaly, Dandy Walker malformation, septal heart defects, muscular VSD, coarctation of the aorta, esophageal atresia, cloacal exstrophy, craniosynostosis and omphalocele. Although we initially observed associations between CC use and hypospadias, adjustment for confounders substantially reduced the effect estimates.

The association between CC and NTDs has been studied and discussed widely with inconsistent findings (Cornel *et al.*, 1990; Mills *et al.*, 1990; Werler *et al.*, 1994; Shaw *et al.*, 1995). A pooled analysis of these studies on CC and NTDs reported a prevalence ratio of 1.08 (95% CI 0.76–1.51), and the authors concluded that 'an increased risk of NTDs due to CC could not be ruled out' (Greenland and Ackerman, 1995). Two recent studies found increased ORs for the association between CC and NTDs. The first study evaluated the odds of spinal NTDs, which included spina bifida occulta, and found a crude OR of 11.7 (95% CI 2.0–44.8; Wu *et al.*, 2006). In a second study of the association between CC use during pregnancy (rather than before) and NTDs, investigators reported a crude OR of 6.4 (95% CI 1.3–31.4); however, after adjustment for confounders this OR was no longer significant (Banhidy *et al.*, 2008). There are no reports in the literature on possible associations between CC and septal heart defects. However, Tulandi *et al.* (2006) reported that among 397 newborns from women treated with CC, 4 had infants with a VSD, which is more than expected. Using a different data set,

Table II Results of crude and adjusted analyses of CC use compared with not using any fertility treatments, National Birth Defects Prevention Study 1997–2005.

Birth defect categories	Unassisted conception	CC	Crude OR[a] (95% CI)	Adjusted OR (95% CI)
Controls	6406	94		
Anencephaly	320	9	1.9 (1.0–3.8)	**2.3 (1.1–4.7)**
Spina bifida	679	9	0.9 (0.5–1.8)	0.8 (0.4–1.8)
Encephalocele	129	4	2.1 (0.6–5.7)	2.7 (0.9–7.6)
Dandy Walker malformation	92	5	**3.7 (1.2–9.3)**	**4.4 (1.7–11.6)**
Hydrocephaly	285	5	1.2 (0.4–2.9)	1.1 (0.4–2.8)
Cataract[b]	203	5	1.6 (0.5–3.9)	1.3 (0.5–3.4)
Anotia/microtia	376	7	1.3 (0.6–2.8)	2.1 (1.0–4.7)
Heterotaxia with heart defects	189	4	1.4 (0.4–3.9)	2.2 (0.8–6.1)
Conotruncal heart defects	1395	16	0.8 (0.5–1.3)	0.7 (0.4–1.2)
D-transposition great vessels	440	3	0.5 (0.1–1.5)	0.4 (0.1–1.4)
Tetralogy of Fallot	619	11	1.2 (0.6–2.3)	1.1 (0.6–2.1)
AVSD	167	3	1.2 (0.3–3.8)	1.1 (0.3–3.5)
Septal heart defects	3246	74	**1.6 (1.1–2.1)**	**1.6 (1.1–2.2)**
Perimembraneous VSD	1302	31	**1.6 (1.1–2.4)**	1.5 (1.0–2.3)
Muscular VSD[b]	165	5	4.2 (0.9–18.3)	**4.9 (1.4–16.8)**
ASD secundum or NOS	1895	39	1.4 (1.0–2.0)	1.5 (1.0–2.3)
Right outflow tract heart defects	1109	18	1.1 (0.7–1.8)	1.0 (0.6–1.7)
Pulmonary valve stenosis[b]	813	16	1.3 (0.7–2.2)	1.3 (0.7–2.2)
Left outflow tract heart defects	1111	33	**2.0 (1.4–3.0)**	1.6 (1.0–2.4)
Coarctation of aorta	583	20	**2.3 (1.4–3.8)**	**1.8 (1.1–3.0)**
Aortic stenosis	234	9	**2.6 (1.2–5.3)**	1.9 (0.9–4.0)
Hypoplastic left heart	335	8	1.6 (0.8–3.4)	1.3 (0.6–2.8)
Choanal atresia	78	4	3.5 (0.9–9.6)	2.7 (0.9–7.8)
Cleft lip with or without palate[b]	1672	26	1.0 (0.7–1.6)	1.1 (0.7–1.8)
Cleft palate[b]	873	10	0.8 (0.4–1.5)	0.8 (0.4–1.5)
Esophageal atresia	373	16	**2.9 (1.7–5.0)**	**2.3 (1.3–4.0)**
Small intestinal atresia	253	4	1.1 (0.3–2.9)	1.4 (0.5–3.8)
Anorectal atresia	582	10	1.2 (0.6–2.3)	1.2 (0.6–2.3)
Biliary atresia	102	3	2.0 (0.4–6.2)	1.4 (0.3–5.8)
Hypospadias, 2nd or 3rd degree[b]	1177	36	**2.3 (1.4–3.5)**	1.5 (0.9–2.3)
Cloacal exstrophy	49	3	4.2 (0.8–13.3)	**5.4 (1.6–19.3)**
Transverse limb deficiencies	392	10	1.7 (0.9–3.4)	1.8 (0.9–3.6)
Craniosynostosis	734	30	**2.8 (1.8–4.2)**	**1.9 (1.2–3.0)**
Diaphragmatic hernia	479	9	1.3 (0.6–2.6)	1.2 (0.6–2.4)
Omphalocele	245	9	**2.5 (1.1–5.0)**	**2.2 (1.1–4.5)**
Amniotic band sequence and limb body wall complex	197	3	1.0 (0.2–3.2)	1.4 (0.4–4.6)

AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; NOS, not otherwise specified; or, odds ratio; CI, confidence interval.
Adjusted for maternal age (continuous), maternal race, parity, previous miscarriages, maternal education, periconceptional smoking, periconceptional alcohol use, obesity and periconceptional folic acid use. Bold indicates statistical significance.
[a]For those with less than five expected in any one cell, Fisher's exact confidence intervals were calculated.
[b]For some defects not all controls were used because of exclusions that applied to the case groups and these same exclusions were applied to the controls; cataracts were not included for all years, 75 exposed controls; Pulmonary valve stenosis was not included in one center for 1 year, 93 exposed controls; muscular VSD was only included 1 year, five exposed controls; orofacial clefts were not included for 1 year for one center, 92 exposed controls; hypospadias only affects males, 44 exposed controls.

we previously identified an association between CC and craniosynostosis: in our earlier paper, we saw a crude OR of 3.8, based on five exposed cases (Reefhuis *et al.*, 2003). There are no reports in the literature about associations between CC and Dandy Walker malformation, coarctation of aorta, esophageal atresia or omphalocele.

The fact that CC is taken before conception has often been cited as evidence against biologic plausibility. However, Mikkelson *et al.* (1986)

and Young et al. (1999) found that zuclomiphene, the more active isomer in CC preparations, accumulates over consecutive cycles and can still be detected in plasma 1 month after administration. Also, using a mouse model, Dziadek (1993) reported an increase in exencephaly among females injected with CC before ovulation in doses similar to those used in humans.

Previous human studies that have investigated the impact of CC on fetal development have been criticized for combining the use of CC with ART. Simpson has postulated that medication for ovulation stimulation may have an independent adverse effect on the developing fetus (Simpson, 1996). We previously published our findings on ART and birth defects (Reefhuis et al., 2009) and found associations with septal heart defects, cleft lip with or without cleft palate, esophageal atresia and anorectal atresia among singleton births. The defect categories that appear to be associated with both CC and ART are septal heart defects and esophageal atresia.

Many of the studies investigating the association between infertility treatments and birth defects have been limited by small numbers and lack of an appropriate control group (Greenland and Ackerman, 1995; Simpson, 1996). Our results are based on data from an ongoing population-based case–control study of more than 30 structural birth defects and multiple maternal exposures. Cases were ascertained through existing surveillance systems, which should limit ascertainment bias based on infertility treatment status. All cases were reviewed by clinical geneticists using standardized case definitions that exclude chromosomal and single-gene conditions, which decreased the etiologic heterogeneity of the case groups. Because we combined data from 10 regions across the USA, our power is higher than that of most other studies. This enabled us to look at individual birth defects, e.g. anencephaly instead of all NTDs combined, and cleft palate alone instead of all orofacial clefts. It also enabled us to control for several potential confounders, including all those recommended by Greenland and Ackerman (i.e. ethnicity, age, obesity, gravidity, folate supplementation; Greenland and Ackerman, 1995).

In the main analysis, we did not adjust for twinning because it is likely in the causal pathway. However, when we limited our analyses to singleton births we observed fewer defects to be associated with CC. This could be related to the smaller numbers, or to the fact that some of the defects identified are associated with twinning, independent of exposure to CC.

We observed the association between CC and hypospadias that was reported in the literature (Meijer et al., 2006) in our crude analyses, but this finding was no longer significant after adjustment for potential confounders. This demonstrates the importance of adjusting for confounders when analyzing exposures that appear to be strongly associated with maternal age and socioeconomic status.

There are two main limitations to this study. The first is the potential for recall bias. Classification of exposure to infertility treatments was based solely on maternal report, and not validated by medical records review. However, we hypothesize that the use of infertility treatments is a highly salient life event that women are likely to accurately report in the time frame of the NBDPS interviews. Another limitation is our inability to separate effects of the underlying subfertility from those of the use of CC. Subfertile women may have a higher risk of having a child with a birth defect regardless of whether infertility treatments are used (Robert and Francannet, 1996; Li, 1999; Zhu et al., 2006). In our study, women were not asked the time to conception or the specific infertility diagnosis, so we were unable to adjust for these factors. We also did not collect information on the presence of polycystic ovary syndrome, a condition for which women are often prescribed CC in order to achieve pregnancy. There is also the possibility of selection bias related to non-participation in the study or to incomplete participation and missing information on the fertility questions. It is possible that women who conceive after taking CC are more likely to participate in the study; however, we would expect that effect to be similar for case-and control-mothers.

In this population-based multi-site case–control study, we found associations between the use of CC and nine defects: Dandy Walker malformation, muscular VSD, cloacal exstrophy, anencephaly, all septal heart defects combined, coarctation of aorta, esophageal atresia, craniosynostosis and omphalocele the first three associations are based on three, five and five exposed cases, respectively, and should be interpreted with caution. It is also possible that our findings arose by chance, considering the large number of comparisons included in this study. Also, given the prevalence of Dandy Walker malformation (1–8 per 100 000 births; Ohaegbulam and Afifi, 2001; Long et al., 2006) and cloacal exstrophy (0.6 per 100 000 births; Caton et al., 2007), the absolute risk of these outcomes would be very low even if these findings are confirmed. Septal heart defects, for which we saw an aOR of 1.6 (95% CI 1.1–2.2), are much more common (4.2 per 1000 births; Reller et al., 2008), such that a 60% increased risk could translate to an absolute risk of 6.7 per 1000 if the association were causal in nature. Of note, septal heart defects can be mild; a significant proportion of VSDs close spontaneously, with no need for surgical or medical intervention (Axt-Fliedner et al., 2006). The prevalence of craniosynostosis is 4.3 per 10 000 births (Boulet et al., 2008), so based on an OR of 1.9 from the present analysis, a 90% increased risk could result in an absolute risk of 8.2 per 10 000 births.

In the USA an estimated 1.6% of pregnancies are conceived with the use of CC (Duwe et al., 2010), reflecting more than 67 000 exposed pregnancies per year. Although the associations we observed in this analysis are limited in magnitude and some are based on small numbers and were seen for the first time, the frequency of CC-exposed pregnancies warrants additional investigations to confirm or refute our findings.

Authors' roles

J.R.: Design, acquisition, analysis and interpretation of the data, drafting and editing the article; M.A.H., S.A.R.: design, acquisition, interpretation of the data and editing the article; L.A.S.: interpretation of the data and editing the article.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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