

Fertility Treatments and Craniosynostosis: California, Georgia, and Iowa, 1993–1997

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ABSTRACT. *Objective.* Craniosynostosis, a malformation caused by premature closure of 1 or more cranial sutures, is a rare birth defect usually of unknown cause; however, it is often associated with advanced maternal age. Because fertility treatments are also associated with increased maternal age, this study investigated the possible association between fertility treatments and craniosynostosis.

Methods. Data from the Birth Defect Risk Factor Surveillance study were used, which included infants who were delivered from 1993 through 1997 in California, Georgia, and Iowa. Cases were defined as infants who had nonfamilial, nonsyndromic craniosynostosis and were ascertained through existing birth defect surveillance systems. Controls, infants without birth defects, were selected from the same regions and time period.

Results. Mothers of 99 case infants and 777 control infants from the 3 study locations participated in this study by completing a telephone interview. Unadjusted analyses showed associations with craniosynostosis for mothers who had used clomiphene citrate (odds ratio[OR]: 3.8; 95% confidence interval [CI]: 1.1–12.3), artificial insemination (OR: 4.2; 95% CI: 0.8–9.4), or assisted reproductive techniques (OR: 4.2; 95% CI: 0.5–27.3).

Conclusions. This is the first study that has found associations between fertility treatments and craniosynostosis. However, the numbers are small; therefore, the results should be viewed with caution. *Pediatrics* 2003; 111:1163–1166; *abnormalities, craniosynostoses, pregnancy, fertility agents, assisted reproductive techniques, artificial insemination, fertilization in vitro, registries.*

ABBREVIATIONS. MACDP, Metropolitan Atlanta Congenital Defects Program; OVST, ovulation stimulation; AI, artificial insemination; ART, assisted reproductive techniques; CC, clomiphene citrate; BDRFS, Birth Defect Risk Factor Surveillance; CT, computed tomography; OR, odds ratio.

Premature closure of 1 or more cranial sutures, or craniosynostosis, is a birth defect that presents as an abnormal head shape. Surgery is often required to prevent increased intracranial pressure and to prevent additional malformation of the

skull. The prevalence of craniosynostosis has been estimated at 3–5 per 10 000 births¹; in the Metropolitan Atlanta Congenital Defects Program (MACDP), it has increased from 2.95 per 10 000 births during the period 1968 through 1975 to 5.16 from 1992 through 1999 (MACDP, unpublished data). Normal suture closure occurs during the period from 22 to 30 years of age; the possible causes of premature suture closure are unknown. Several potential risk factors for craniosynostosis have been identified in previous epidemiologic studies: maternal white race,² advanced maternal age,² male infant sex,² maternal smoking,^{3–5} maternal residence at high altitude,⁶ nitrosatable drugs,⁷ and certain paternal occupations.⁸ Recently, genetic associations have also been identified by the discovery of the association between a mutation in the fibroblast growth factor receptor 3 and isolated coronal synostosis.^{9,10}

In 1995 in the United States, an estimated 6.7 million women aged 15 to 44 years had a fertility problem. Of these women, an estimated 2.8 million had used infertility services. Ovulation stimulation (OVST) was mentioned by 34.7% of the women who had used infertility services, artificial insemination (AI) was mentioned by 12.7%, and assisted reproductive techniques (ART) were mentioned by 1.6%.¹¹

The first-line drug of choice for OVST is clomiphene citrate (CC). From 1973–1991, the number of prescriptions for CC nearly doubled.¹² An analysis in a Colorado health maintenance organization from October 1996 through December 1999 found that CC was used in 2.1% of all pregnancies.¹³ Because of the increases that have occurred in craniosynostosis prevalence, maternal age at pregnancy, and use of fertility treatments and because craniosynostosis and fertility treatments both are associated with advanced maternal age, we investigated whether a potential relationship existed between fertility treatments (CC, AI, and ART) and craniosynostosis.

METHODS

We used data from the Birth Defect Risk Factor Surveillance (BDRFS) study. The BDRFS was conducted in San Francisco and Santa Clara counties in California, metropolitan Atlanta in Georgia, and the entire state of Iowa. Approval for the study was obtained from Institutional Review Boards in each of the 3 locations. An outline of the study methods was published earlier.¹⁴

The BDRFS included numerous types of birth defects, but this analysis was restricted to case infants with craniosynostosis and all control infants. Case infants with chromosomal anomalies or recognized syndromes were excluded. Case infants whose mothers reported a first-degree family history of craniosynostosis were also excluded. All case records were reviewed by a clinical geneticist at each site and were classified as either isolated (a solitary major primary defect, meaning no other major defect in other

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organ systems) or multiple (at least 1 additional unrelated, major, and specified defect). Control infants were liveborn infants with no major birth defects.

In California, case infants were ascertained using the population-based California Birth Defects Monitoring Program, a surveillance system that also uses active case finding.¹⁵ This study included cases from all hospitals and genetic clinics in 2 counties (San Francisco and Santa Clara) in the San Francisco Bay area. Case and control infants were limited to infants who were born during the period January 1993 through July 1996 to mothers who were residents of these 2 counties. Control infants were selected randomly from birth hospitals, with the proportion selected from each hospital based on the proportion of the total births in the 2 counties that occurred in that hospital. These 2 counties have approximately 40 000 annual births.¹⁶ Additional details of the California component of the BDRFS have been described elsewhere.¹⁷

In Georgia, case infants were ascertained using the population-based MACDP. This surveillance system uses active case finding among records of all birth hospitals in metropolitan Atlanta to identify affected infants (live births and stillbirths >20 weeks' gestation) and includes a clinical review of each abstracted case record.¹⁸ Case infants were also ascertained from the 2 pediatric referral hospitals in Atlanta, 1 genetics laboratory, and vital records. Control infants were a stratified random sample of births at the 18 birth hospitals used for case ascertainment by MACDP. To be eligible for inclusion as either a case or a control infant, infants had to be born during the period January 1993 through August 1997 and the mother had to be a resident of 1 of the 5 metropolitan Atlanta counties (Clayton, Cobb, Dekalb, Fulton, or Gwinnett) at the time of delivery. There were approximately 40 000 annual births to residents of these 5 counties during this period.

In Iowa, cases were ascertained using the population-based Iowa Birth Defects Registry, a surveillance system that uses active case finding to ascertain birth defects in the entire state.¹⁹ Case infants were ascertained from 138 birth hospitals, 2 pediatric hospitals, 1 genetics laboratory, the Iowa Department of Public Health vital records, and 16 regional genetics clinics. Control infants were selected using birth certificates. Both case mothers and control mothers were limited to residents of Iowa who delivered during the period January 1993 through December 1995. An average total of 37 217 annual births to Iowa residents occurred during this period.

All 3 locations used the same interview instrument and completed a telephone interview (approximately 1 hour) with mothers of case and control infants. The interview included questions on maternal health and medication use, pregnancy history and fertility, demographics, family history, nutrition, occupational and environmental exposures, tobacco use, alcohol use, and substance abuse. Interviews were conducted in either English or Spanish. Mothers who did not speak English or Spanish were excluded.

Variables that were studied in this investigation included whether the pregnancy was intended; the couple used any assistance (male or female) to get pregnant; the couple used surgical fertility procedures (such as the reopening of the fallopian tube); or the couple used OVST, AI, or ART. We had no access to fertility treatment medical records. Exposure to OVST was defined as any reported use from 3 months before until 3 months after conception. Mothers were specifically asked about CC and any other medications that they might have used to help them become

pregnant. Use of ART included in vitro fertilization-embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, pronuclear stage transfer, and tubal embryo transfer. OVST is often used in conjunction with AI or ART. Mothers who used OVST in combination with AI or ART were excluded from the OVST category.

Data from the 3 sites were combined, and unadjusted analyses were conducted using SPSS 10.0. When the expected number in 1 or more of the cells of the contingency tables was <5, the Fisher exact test was used.

We evaluated the association between craniosynostosis and whether the pregnancy was intended; whether there was any fertility assistance; the use of surgical fertility procedures; the use of any OVST; and the use of CC, AI, and ART. Factors were considered as potential confounders on the basis of a priori information or when they were associated with both craniosynostosis and maternal age in our data set. Because sparse data made it impossible to control for potential confounders in a multivariate model, analyses were performed for subsets of the data to assess the impact of the potential confounders. Analyses were also done for the subsets of isolated cases of craniosynostosis, for all cases excluding lambdoidal craniosynostosis, and for cases diagnosed using either a computed tomography (CT) scan or skull radiograph.

RESULTS

Information from 99 case and 777 control mothers was analyzed: 24 cases and 195 controls from California, 47 cases and 247 controls from Iowa, and 28 cases and 335 controls from Georgia. Of the 99 case infants, 38 had sagittal craniosynostosis (the most common phenotype), 22 had lambdoidal craniosynostosis, 9 had coronal craniosynostosis, 8 had metopic craniosynostosis, and 22 had unspecified or mixed types of craniosynostosis. CT scans were used to diagnose 21 case infants, skull radiographs were used to diagnose 15. For 52 case infants, the only available diagnostic information was that craniosynostosis was surgically corrected. For 11 case infants, the diagnostics were unclear or the diagnostic information was missing.

Multiple births, non-Hispanic white maternal race, and male infants were more common among cases than controls (Table 1). No differences were observed for maternal age, maternal education, smoking, or gravidity.

Unadjusted analyses examined intended pregnancies and the use of fertility treatments in association with craniosynostosis (Table 2). That the pregnancy was intended was positively associated with craniosynostosis. This was also true for the use of any fertility assistance by the couple. Surgical fertility procedures were not associated with craniosynostosis. The use of CC, AI, and ART showed associations

TABLE 1. Demographic Characteristics of Craniosynostosis Case Infants and Control Infants in California, Georgia, and Iowa, 1993–1997

	Cases (N = 99)		Controls (N = 777)		χ^2 P Value
	n	%	n	%	
Mean maternal age (y)	28.3		28.2		
Maternal age \geq 35 y	15	15	115	15	.91*
Maternal education >12 y	63	64	497	64	.89*
Maternal smoking (any vs none)	21	21	134	17	.34*
Primigravida	55	56	475	61	.32*
Multiple births	5	5	17	2	.09
Maternal race, white	87	88	495	64	.001*
Infant sex, male	70	71	410	53	<.001*

* Asymptotic χ^2 tests.

TABLE 2. Crude ORs From Unadjusted Analyses for Exposure to Different Fertility Treatments and Craniosynostosis, California, Georgia, and Iowa, 1993–1997

	Yes		No		OR	95% CI
	Cases	Control	Cases	Control		
Index pregnancy was intended	70	418	29	357	2.1	1.3–3.3†
Used fertility assistance	10	31	89	744	2.7	1.3–5.7‡
Surgical Procedures	1	7	98	770	1.1	0.1–9.2
OVST only*	5	14	89†	753†	3.0	0.9–9.3
CC only*	5	11	89†	753†	3.8	1.1–12.3
AI	3	6	89†	753†	4.2	0.8–19.4
ART	2	4	89†	753†	4.2	0.5–27.3
CC or AI or ART	10	21	89†	753†	4.0	1.6–9.3

CI indicates confidence interval.

* CC is a subset of OVST; infants were included in these 2 categories only when the mother did not use AI or ART with the OVST.

† Infants were considered not exposed when their mothers did not use OVST, AI, or ART.

‡ Asymptotic confidence intervals.

both separately and combined (odds ratio [OR]: 4.0; 95% confidence interval: 1.6–9.3).

Analyses were done on subgroups of the data set for the potential confounders maternal age (<35 and ≥35), white maternal race, singleton births, and mothers who did not smoke. Data were too sparse to allow for simultaneous adjustment (Table 3). Most ORs in the subgroup analyses were from 2 to 4. However, among younger mothers and nonsmoking mothers, the association between CC and craniosynostosis was stronger. The results of the subgroup analyses for the isolated and nonlambdoidal cases and diagnostic methods are also listed in Table 3.

DISCUSSION

In this study, women who reported use of fertility treatments were more likely to deliver an infant with craniosynostosis. The use of CC was associated with a 3- to 4-fold increase in craniosynostosis. CC has been studied in association with neural tube defects, with mixed results. A meta-analysis of 10 of these epidemiologic studies of CC and neural tube defects concluded that an elevation in neural tube defect risk could not be ruled out, but any elevation would probably be less than 2-fold.²⁰

The crude association between use of ART and craniosynostosis revealed a 3- to 4-fold increase; however, the data are very sparse, resulting in imprecise estimates. Previous studies investigating

ART and any birth defects found both null^{21,22} and elevated²³ risks. However, the total numbers of infants with birth defects in these investigations were small (150–250), rendering analyses of rare specific defects such as craniosynostosis too imprecise to draw firm inferences.

In this study, we combined data from 3 sites, leading to a relatively large number of cases for such a rare defect. However, wide confidence intervals resulted from the combination of this rare defect and rare exposures.

Contrary to the results in the literature, our data did not show an association between increased maternal age and craniosynostosis. The reason is not clear, but it is possible that younger mothers are less likely to participate in studies such as these, or it could be attributable to chance. Alternatively, the associations previously reported between maternal age and craniosynostosis actually might have been attributable to other unmeasured exposures, such as fertility treatments.

There was a higher-than-expected rate of lambdoidal craniosynostosis: 22 of the 99 case infants had lambdoidal craniosynostosis. Because this is higher than the expected rate (2%–5%),¹ we also conducted the analyses excluding the lambdoidal cases. The results of these analyses were very similar to the crude analyses (Table 3).

The available information on the diagnostics was

TABLE 3. Crude and Subgroup Analyses for Potential Confounders for Each of the 3 Fertility Treatments of Craniosynostosis in California, Georgia, and Iowa, 1993–1997

Category	CC*		AI*		ART*	
	OR	95% CI	OR	95% CI	OR	95% CI
All (crude analysis)	3.8	1.1–12.3	4.2	0.8–19.4	4.2	0.5–27.3
Maternal/infant subgroups						
Maternal age <35 y	5.5	1.1–23.5	3.2	0.3–20.4	—†	—†
Maternal age ≥35 y	1.9	0.0–19.7	9.7	0.1–770.3	19.5	0.9–1157.5
Only non-Hispanic white mothers	2.8	0.7–8.9	2.0	0.2–11.5	3.0	0.3–21.5
Only singleton births	3.2	0.7–10.9	3.5	0.3–21.5	17.3	0.9–1024.4
Only nonsmokers	4.5	1.2–14.8	4.5	0.7–21.4	2.2	0.0–23.0
Diagnostic subgroups						
Isolated craniosynostosis	3.5	0.8–12.0	4.8	0.8–22.8	2.4	0.1–24.4
Excluding lambdoidal craniosynostosis	4.0	0.9–14.0	5.5	0.9–26.5	5.5	0.5–39.3
Only CT scan or radiograph diagnostics	9.4	2.1–34.2	4.3	0.1–37.4	13.0	1.12–93.9

* CC, AI, and ART are mutually exclusive categories. Mothers with CC and AI or CC and ART are included only as exposed to either AI or ART.

† There were no cases whose mother was younger than 35 years of age and who used ART.

limited; CT scans and skull radiographs are considered the gold standard, so we also conducted the analyses using only cases that were diagnosed using 1 of these 2 methods. The ORs for CC and ART were higher for this subset of cases than the crude ORs for all cases combined (Table 3).

Pregnancies that are exposed to fertility treatments differ from those that are not exposed in several ways. First, there is the possibility of confounding by indication. We did not have information on the underlying subfertility diagnosis. That is, the underlying fertility problem, rather than the treatment, could be associated with craniosynostosis. That we found similar ORs for the different fertility treatments could suggest an underlying cause or could indicate the effect of OVST, which is used in all 3 types of fertility treatments.

Second, there might be exposures that are associated with both infertility and craniosynostosis. For example, several environmental exposures (smoking, alcohol, solvent mixtures, and chlorinated hydrocarbons) are associated with infertility.²⁴ At least 1 of these exposures (maternal smoking) has also been associated with craniosynostosis. However, for 1 of these other factors to explain the 3- to 4-fold risks observed for CC, it would have to be very strongly associated with craniosynostosis. In addition, in our data, there does not seem to be an association between smoking and craniosynostosis (Table 1).

Third, women who use fertility treatments differ in socioeconomic status from women who do not. The only information that we had on socioeconomic status was the education of the mother, which has been demonstrated to be a good surrogate for socioeconomic status.²⁵ This showed no association with craniosynostosis or the fertility treatments in our study.

The last general difference between pregnancies conceived with fertility treatments and pregnancies conceived naturally is that the first are very desired pregnancies, which might lead to a more health-conscious pregnancy. This would be expected to attenuate any observed risks. However, parents who use fertility treatments might be more likely to seek treatment for a mild case of craniosynostosis sooner than parents who do not use fertility treatments.

The underlying mechanisms for the observed association are unknown. The embryologic timing of many of these fertility treatments predates what is likely to be a critical fetal developmental period, casting some doubt on the biological plausibility of some of the findings. However, CC exposure might have occurred postconceptionally, resulting in direct exposure during a relevant embryologic time period.

This is the first study that found an association between fertility treatments and craniosynostosis. Although increased risks were found, estimates were imprecise. Results should be viewed with caution and confirmed with additional studies of infants who are born after fertility treatments.

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