

Reefhuis J et al: Fertility treatments and craniosynostosis : California, Georgia, and Iowa, 1993-1997. *Pediatrics*, 2003, 111, 1163-66

Type of study	Population based case-control, specific for craniosynostosis
Where	California, Georgia, Iowa
When	1993-1997
Cases	99 infants who had nonfamilial, nonsyndromic craniosynostosis ascertained through birth defect surveillance systems Case infants with chromosomal anomalies, recognized syndromes, whose mothers reported a first-degree family history of craniosynostosis were excluded. All case records were reviewed by a clinical geneticist at each site
Case prevalence among the population	5.2 per 10,000 births from 1992 through 1999 (Metropolitan Atlanta Congenital Defects Program)
Controls	777 liveborn infants with no major birth defects, selected from the same regions and time period (California: selected randomly from birth hospitals; Georgia: a stratified random sample from birth hospitals; Iowa: selected using birth certificates)
Exposure definition	Exposure to ovulation stimulation was defined as any reported use from 3 months before until 3 months after conception. Mothers were specifically asked about clomiphene citrate and any other medications used to help them become pregnant
Ascertainment of drug exposure	All 3 locations used the same interview instrument and completed a telephone interview (1 hour) with mothers of case and control infants.
Prevalence of exposure among controls	11: 777 (1.4%)
Analysis	Data from the 3 sites were combined; unadjusted and control for potential confounders analyses were performed for subsets of the data (maternal age, white maternal race, singleton births, mothers who did not smoke)
Strengths	<ul style="list-style-type: none"> - All case records were reviewed by a clinical geneticist at each site - Standardized interviews - Analyses for specific sub-groups of defects (for the subsets of isolated cases of craniosynostosis, for all cases excluding lambdoidal craniosynostosis, for cases diagnosed using either a computed tomography scan or skull radiograph)
Weaknesses	<ul style="list-style-type: none"> - The numbers are small (wide CI resulted from the combination of both rare defect and exposure) - Drug intake was based on maternal interview (risk of recall bias) - Control liveborn infants with no birth defects (risk of recall bias) - For many case infants the diagnosis information was incomplete, unclear or missing - Possibility of confounding by indication (the underlying fertility problem, rather than the treatment, could be associated with craniosynostosis) - The time of the interview after delivery was not indicated - Not indicated if the interviewers were aware of the case and control status - No information about dosages
Main results	Unadjusted analyses showed an association with craniosynostosis for mothers who had used clomiphene citrate (OR 3.8, 95%CI 1.1-12.3)

