



TEXAS

Department of State Health Services
Birth Defects Epidemiology and Surveillance

BIRTH DEFECT RISK FACTOR SERIES: CRANIOSYNOSTOSIS

INTRODUCTION

Definition

Craniosynostosis is premature closure of any of the cranial sutures. That is, the bones of the fetal skull fuse together before delivery. This syndrome can affect one suture or multiple sutures (sagittal, metopic, coronal, or lambdoid), and often results in an abnormally shaped head [1].

Craniosynostosis cases are categorized in several ways. Cases involving one suture are classified as simple; multiple suture cases are classified as complex [2]. Unlike secondary craniosynostosis, which results from disorders like hyperthyroidism and brain growth anomalies, primary craniosynostosis is not secondary to other underlying problems [2, 3]. Studies frequently distinguish between nonsyndromic (isolated) craniosynostosis, which occurs without other major defects, and syndromic craniosynostosis, which may have multiple associated defects, particularly of the limbs and face [2, 4]. Nonsyndromic cases account for about 85% of all craniosynostoses.

Craniosynostosis is associated with more than 180 syndromes [2]. Some of the more common ones include Crouzon syndrome, Muenke syndrome, Apert syndrome (Acrocephalosyndactyly Type I), Carpenter syndrome (Acrocephalosyndactyly Type II), Saethre-Chotzen syndrome (Acrocephalosyndactyly Type III), and Pfeiffer syndrome (Acrocephalosyndactyly Type IV). Because many of these syndromes have known genetic causes, many studies focus on elucidating risk factors for nonsyndromic cases of craniosynostosis.

About one half of children with nonsyndromic craniosynostosis demonstrate speech, cognitive, or behavioral abnormalities [5]. Syndromic craniosynostosis may be associated with more severe deficits [2, 6].

Prevalence

The birth prevalence in Texas for 1999-2008 deliveries was 4.53 cases per 10,000 live births [7]. Birth prevalence in the United States for craniosynostosis is not currently known.

Many craniosynostosis studies report that sagittal synostosis is most common [1, 8-16]. The lambdoid suture is rarely affected [9-14]. A few studies have reported a larger proportion of lambdoidal craniosynostosis cases than expected [1, 15, 17], but this has been found to be due to regional differences in case ascertainment [15, 18].

GENETIC FACTORS

Although the etiology for most nonsyndromic craniosynostoses is unknown, many syndromic cases are caused by single-gene mutations or chromosomal abnormalities [2, 19]. Mutations in fibroblast growth factor receptor (FGFR) and TWIST1 genes are responsible for common forms of syndromic craniosynostosis [2]. FGFR2 mutations can cause Apert, Crouzon, Jackson-Weiss, and Beare-Stevenson syndromes. Pfeiffer syndrome results from mutations in FGFR1 or FGFR2, and a specific mutation in FGFR3 (P250R) causes Muenke syndrome. Mutations in TWIST1 cause most cases of Saethre-Chotzen syndrome. FGFRs 1-3 and TWIST1 are involved in bone and tissue formation in the head and limbs during embryonic development [20]. Other syndromic forms of craniosynostosis have been linked to mutations in EFNB1 (craniofrontonasal dysplasia), RAB23 (Carpenter syndrome), RECQL4 (Baller-Gerold syndrome), POR (Antley-Bixler syndrome) and MSX2 (Boston-type craniosynostosis) [2]. Genetically identical mutations may result in a wide variety of phenotypes.

Autosomal dominant inheritance with variable expression is seen with most common syndromic forms of craniosynostosis. A small percentage of nonsyndromic craniosynostoses have been found to be inherited,

especially those with coronal suture involvement [21, 22]. Because genetic mutations are found more frequently in cases of coronal synostosis, genetic testing is suggested for syndromic craniosynostosis cases and nonsyndromic coronal synostosis cases [2, 19, 23].

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Trends

Craniofacial centers in Europe and the United States have reported recent increases in metopic synostosis [10, 14, 16, 24], although one population-based study did not share this finding [8]. Although changes in lambdoidal craniosynostosis prevalence have also been reported [8, 15], these trends warrant careful interpretation because acquired plagiocephaly is easily misdiagnosed as lambdoidal craniosynostosis [25].

Ethnicity

No clear association has been seen between ethnicity and craniosynostosis risk. Non-Hispanic white maternal ethnicity has been associated with an increased risk for having a child with craniosynostosis [1, 9, 12, 13]. Studies have also found a lower risk for black or non-white mothers [8, 26]. However, one investigation found no significant effect of ethnicity on craniosynostosis risk [15]. Foreign-born Hispanic mothers may have a decreased risk of having a child with craniosynostosis compared to Hispanic mothers born in the United States [27]; however, this association may be limited to recent immigrants [28].

Parental Age

Craniosynostosis risk appears to increase with increasing maternal age [8, 9, 12, 26, 29, 30]; however, some studies did not find a significant relationship between maternal age and craniosynostosis risk [1, 15]. The relationship between father's age and craniosynostosis risk is less clear. One study identified older age of the father as a risk factor [15], but other studies did not [26, 31]. Increased age of the father has been linked to some craniosynostosis syndromes [32, 33].

The risk of craniosynostosis associated with parental age may vary by the suture involved. For example, two studies found older maternal or paternal age to be a risk factor for coronal synostosis [22, 34]. Other studies found no association between increased parental age and sagittal or metopic synostosis [35-37]; however, one study contradicts these findings [8].

Parental Education

Studies of parental education have yielded inconsistent results. A higher level of maternal education has been linked to craniosynostosis [9, 12], but other studies have not found an association between maternal or paternal education and the risk of craniosynostosis [1, 26, 34].

Infant Sex

Most studies have reported higher craniosynostosis rates or ratios among male infants, particularly for sagittal and metopic synostosis [1, 8, 11-15, 24, 26, 34-39]. Coronal craniosynostosis seems to be more common in female infants [8, 11, 14, 22]; however, not all studies have observed this association [15, 34].

Fetal Constraint-Related Factors

It has been hypothesized that some cases of craniosynostosis may be related to fetal head constraint in the womb [13, 40, 41]. Possible constraint-related factors like gestational age, birth weight, parity, plurality, and certain obstetric factors have been studied for associations with craniosynostosis risk.

Gestational age as a risk factor for craniosynostosis has mixed results. Some studies have found an increased risk of craniosynostosis associated with preterm birth [12, 13, 15], but others have not found gestational age to be a risk factor [8, 26]. Both high and low infant birth weights have been associated with increased risk of craniosynostosis [8, 12, 13, 26], although in one study birth weight was no longer a significant risk factor after consideration of gestational age in the analysis [15]. Craniosynostosis risk related to birth weight varies by the suture involved, although not consistently [8, 13, 15, 36, 37].

Several studies have not found parity to be a risk factor overall for craniosynostosis [8, 9, 13, 26]. Other studies have reported associations between parity and craniosynostosis risk that have been inconsistent [13, 30, 34]. Evaluation of the impact of plurality on craniosynostosis risk has produced mixed results, with some studies reporting increased risk of the defect for multiple births [8, 9, 12, 26] while others found no association [1, 13, 15, 42]. Gravidity and previous pregnancy termination have not been found to be risk factors [1, 12, 26].

Certain obstetric factors, like birth presentation, may be linked with increased craniosynostosis risk [15]. Delivery method has not been linked to craniosynostosis risk [15].

FACTORS IN LIFESTYLE OR ENVIRONMENT

Parental Occupation

Occupation of the father in the agriculture and forestry or mechanics and repairman fields has been suggested as a risk factor for craniosynostosis [43]. While one study found an increased risk of having a child with craniosynostosis for women employed as administrative support personnel [44], another found no association of maternal occupation with craniosynostosis risk [43]. Maternal or paternal military service since 1990 does not appear to be a risk factor for craniosynostosis [45].

Place of Residence

Place of residence has not been found to affect craniosynostosis risk, except for a decreased risk for lambdoid synostosis in rural areas [15, 26]. Overall, altitude exposure has not been associated with an increased risk of craniosynostosis [26, 42]. However, mothers who live or work at high altitudes and smoke may have an increased risk for having a child with craniosynostosis, especially for coronal and metopic synostosis [42].

Maternal Health

Mothers who are overweight may be at an increased risk for delivering a child with isolated craniosynostosis [46], but another study failed to confirm this finding [47]. Although maternal pre-gestational diabetes mellitus has not been found to be a risk factor for craniosynostosis, gestational diabetes mellitus may confer an increased risk for having a child with craniosynostosis and multiple additional defects [48]. Maternal thyroid disease has been reported as a risk factor for craniosynostosis [12]. No associations have been found for maternal genital tract infections or dietary glycemic intake and craniosynostosis risk [49, 50].

Smoking

Studies have found that maternal smoking is associated with an increased risk of infant craniosynostosis [17, 34, 51]. One study found this association only for heavy smokers who continued smoking after the first trimester and had delayed or no folic acid supplement use [52]. Another study did not report smoking as a risk factor [30].

Drugs and Medication

Studies of maternal alcohol consumption have had mixed results. One study found no relationship between maternal alcohol consumption and craniosynostosis risk [17]. However, one study found risk to be inversely related to alcohol consumption after the first trimester, and another found an inverse relationship between alcohol consumption and risk of sagittal synostosis [37, 53]. High levels of caffeine consumption may confer an increased risk for craniosynostosis, although lower amounts showed no association [54].

There may be a connection between nitrosatable drugs (chlordiazepoxide, nitrofurantoin, and chlorpheniramine) and increased risk of craniosynostosis [30]. However, one study found an increased risk only for cases of sagittal and lambdoidal synostosis [55], and another failed to find an association between nitrofurantoin and craniosynostosis [56].

Evidence is also inconclusive as to whether selective serotonin reuptake inhibitors (SSRIs)—typically used to treat depression—are associated with an increased risk for this defect. One study found an increased risk of craniosynostosis with SSRI use, particularly among obese women; when examining specific SSRIs, fluoxetine was associated with increased craniosynostosis risk [57]. However, two other studies did not support these findings [58, 59].

Use of antihistamines during early pregnancy, specifically diphenhydramine, may be a risk factor for craniosynostosis [60]. Although treatment for maternal thyroid disease may be linked to an increased risk of infant craniosynostosis [12], one study found no association between maternal use of thyroxine and craniosynostosis risk [30].

Valproic acid and other anticonvulsants have been linked to increased craniosynostosis risk [30, 61]. Specifically, a relationship has been suggested between valproic acid exposure and metopic synostosis [62]. However, one study reported no association between valproic acid use and craniosynostosis risk [55].

No associations have been found between craniosynostosis risk and use of the following substances:

- analgesics, including acetaminophen, codeine, and hydrocodone [30, 63, 64]
- antibacterial drugs, including penicillins, erythromycins, sulfonamides, and cephalosporins [30, 56]
- antifungal drugs [65]
- oral contraceptives [66]
- illicit drugs, including cannabis, cocaine, and stimulants [55, 67]
- weight loss products, including ephedra [68]
- spermicides [69]

Fertility Treatments

Some evidence exists for a link between specific fertility treatments and greater risk of craniosynostosis. Clomiphene citrate, a drug used for ovulation stimulation, was associated with an increased craniosynostosis risk in two studies [1, 70]. However, one study found no association between craniosynostosis risk and infertility treatment or ovulation stimulation [30]. No studies have found a statistically significant association of craniosynostosis with assisted reproductive technology (ART), such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), or with surgical fertility treatments [1, 71, 72].

Vitamins and Nutrients

Vitamins and dietary nutrients have been studied for their associations with craniosynostosis risk. In one study, higher maternal intake of riboflavin, vitamin B₆, vitamin E, and vitamin C before and during pregnancy was associated with a decreased risk for sagittal synostosis, and higher intake of methionine and vitamin C was associated with a decreased risk for coronal synostosis [9]. In the same study, an increased risk of metopic synostosis was reported with higher intake of choline and vitamin B₁₂. Previous studies of multivitamin usage have not demonstrated a link to craniosynostosis risk [30, 55]. There does not appear to be a protective effect from folic acid supplementation [9]; in fact, one unusual finding indicated an increased risk of craniosynostosis with folic acid taken in the first trimester [30]. However, small numbers limit the strength of this finding.

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*

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