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Craniosynostosis and Risk Factors Related to Thyroid Dysfunction

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Abstract

Thyroid disease is a common problem among women of reproductive age but often goes undiagnosed. Maternal thyroid disease has been associated with increased risk of craniosynostosis. We hypothesized that known risk factors for thyroid disease would be associated with risk of craniosynostosis among women not diagnosed with thyroid disease. Analyses included mothers of 1,067 cases and 8,494 population-based controls who were interviewed for the National Birth Defects Prevention Study. We used multivariable logistic regression to estimate adjusted odds ratios (AOR) and 95% confidence intervals (CI). After excluding women with diagnosed thyroid disease, younger maternal age (AOR 0.7, 95% CI 0.6–0.9, for <25 years versus 25–29), black or other race-ethnicity (AOR 0.3, 95% CI 0.2–0.4 and AOR 0.6, 95% CI 0.4–0.8, respectively, relative to non-Hispanic whites), fertility medications or procedures (AOR 1.5, 95% CI 1.2–2.0), and alcohol consumption (AOR 0.8, 95% CI 0.7–0.9) were associated with risk of craniosynostosis, based on confidence intervals that excluded 1.0. These associations with craniosynostosis are consistent with the direction of their association with thyroid dysfunction (i.e., younger age, black race-ethnicity and alcohol consumption are associated with reduced risk and fertility problems are associated with increased risk of thyroid disease). This study thus provides support for the hypothesis that risk factors associated with thyroid dysfunction are also associated with risk of craniosynostosis. Improved understanding of the potential association between maternal thyroid function and craniosynostosis among offspring is important given that

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craniosynostosis carries significant morbidity and that thyroid disease is under-diagnosed and potentially modifiable.

Keywords

craniosynostosis; thyroid; birth defects

INTRODUCTION

Thyroid disease is a common condition among women of reproductive age. Hypothyroidism affects 2–5% of pregnant women, whereas current or past hyperthyroidism (primarily Graves' disease) affects about 1% [Laurberg et al., 1998; Casey et al., 2006]. Presence of anti-thyroid antibodies is much more common, observed in 13% of pregnant women without recognized thyroid disease in a large US study [Haddow et al., 2010]. Even in the absence of overt thyroid disease, these antibodies are associated with higher levels of thyroid stimulating hormone (TSH) and are predictive of the development of overt thyroid disease. In addition, transient hyperthyroidism (thyrotoxicosis) affects up to 3% of women during early pregnancy, due to the TSH-like activity of placental hCG (human chorionic gonadotropin) [Glinoer, 1998]. Hypo- and hyperthyroidism, as well as the presence of anti-thyroid antibodies in the absence of thyroid disease, are associated with increased risk of adverse pregnancy outcomes such as spontaneous abortion and preterm delivery [van den Boogaard et al., 2011; He et al., 2012; Mannisto et al., 2013]. Improved understanding of the association of maternal thyroid function with reproductive outcomes is particularly important given that thyroid disease often goes undiagnosed [Hollowell et al., 2002], and the appropriate approach to screening and management of thyroid disease during pregnancy is a topic of ongoing debate [Stagnaro-Green and Pearce, 2012].

Craniosynostosis (CS), the premature fusion of one or more cranial sutures, leads to abnormal craniofacial form and function. It may be associated with increased intracranial pressure leading to abnormal neurocognitive development, and most affected infants require extensive reconstructive surgery [Speltz et al., 2004; Rasmussen et al., 2008; Starr et al., 2012]. Wehypothesize that maternal thyroid hormones or anti-thyroid antibodies may result in exposure of fetal tissues to excessive amounts of thyroid hormone, which in turn may cause premature suture fusion. A variety of case-only studies suggest that thyroid hormones may be associated with craniosynostosis [Penfold and Simpson, 1975; Johnsonbaugh et al., 1978; Daneman and Howard, 1980; Cove and Johnston, 1985; Leonard et al., 1987; Stevenson and Trent, 1990; Nishihara et al., 2006].More recently, Rasmussen et al. reported an association of thyroid disease with risk of craniosynostosis using data from the National Birth Defects Prevention Study [Rasmussen et al., 2007]. One explanation for these findings is that thyroid hormones stimulate osteogenesis. In particular, treatment with thyroid hormones has been shown to stimulate osteogenesis of the skull and premature narrowing of cranial sutures in experimental studies [Akita et al., 1994].

Many risk factors for thyroid disease have been identified, such as older maternal age, white or Hispanic race-ethnicity, and higher body mass index [Hollowell et al., 2002; Knudsen et

al., 2005]. In this study, we examined whether risk factors for thyroid disease, among mothers who did not report having thyroid disease, were associated with increased risk of craniosynostosis.

METHODS

Study Design and Data Collection

This study included data on deliveries that occurred from 1997 to 2007 and were part of the NBDPS, a case-control study of birth defects that was conducted in ten states of the U.S. Details about study design and methods have been published [Cogswell et al., 2009; Yoon et al., 2001]. Most study sites included liveborn infants, fetal deaths (at greater than 20 weeks gestation), and electively terminated cases. Each site selected a population-based set of nonmalformed, liveborn control infants during each study year from birth certificates or birth hospitals.

Information on case infants was obtained from hospital reports and medical records [Rasmussen et al., 2003], and one clinical geneticist (SAR) provided a final review of all cases to ensure that they all met standard eligibility criteria. All craniosynostosis cases were verified by radiographic imaging (e.g., skull radiograph or head CT) or surgery. Infants with recognized or strongly suspected single-gene disorders or chromosomal abnormalities were ineligible. The specific suture(s) involved was also identified (i.e., sagittal, coronal, metopic, lambdoid, multiple, or unknown). Infants with more than one type of involved suture (e.g., sagittal and coronal sutures both prematurely closed) were counted only in the multiple suture category.

Maternal interviews were conducted using a standardized, computer-based questionnaire by telephone, in English or Spanish. Interviews were conducted with 71% of eligible case mothers and 66% of eligible control mothers. The median time from delivery to interview was 14 months for cases and 8 months for controls.

Study Variables

Maternal thyroid disease was based on a mother's report of a thyroid disorder or taking thyroid medication at any time during pregnancy [Rasmussen et al., 2007]. This information was in response to general questions about medical conditions; questions specifically about thyroid disease were not asked. We examined the association of craniosynostosis with the following factors related to maternal thyroid dysfunction: maternal age, race-ethnicity, parity, pre-pregnancy body mass index (BMI), fertility medications or procedures (as a proxy for fertility problems), previous miscarriages, diabetes, hypertension, intake of anti-depressants (a proxy for depression) or iron-only supplements (a proxy for anemia), smoking, and alcohol consumption [Glinoer 1998; Hollowell et al., 2002; Belin et al., 2004; Knudsen et al., 2005; Zimmermann et al., 2007; Ashoor et al., 2010; Carle et al., 2012a; Carle et al., 2012b; De Groot et al., 2012; Wu et al., 2013].

Analysis

First, we examined the association of maternal thyroid disease with craniosynostosis, given that our previous analysis of this study question only included data on births through 2002 [Rasmussen et al., 2007]. The current analysis was adjusted only for maternal age, as was done for the previous study. We used logistic regression to estimate odds ratios (OR) and 95 percent confidence intervals (CI). Second, we examined the association of each covariate with maternal report of thyroid disease among the controls, using Chi-square tests. Third, we conducted logistic regression models that included all covariates but that excluded women who reported thyroid disease, to determine the independent association of each covariate with craniosynostosis. We examined associations with craniosynostosis overall and with each suture type separately.

RESULTS

There were 1,067 cases and 8,494 controls available for analysis. The sagittal suture was affected in 566 (53%) cases, the metopic suture in 194 (18%), the coronal suture in 187 (18%), the lambdoid suture in 32 (3%), multiple sutures in 85 (8%), and unspecified in three (0.3%). A total of 37 case mothers (3.5%) and 191 control mothers (2.3%) reported thyroid disease. Most women with thyroid disease did not specify the type of thyroid disease (81% of affected case mothers, 87% of affected control mothers), and many women with thyroid disease did not report intake of a specific thyroid-related medication (19% of cases, 35% of controls). Among those that did report taking a medication, most reported taking levothyroxine (93% of cases, 94% of controls). The adjusted OR for craniosynostosis and maternal thyroid disease was 1.4 (95% CI 0.9, 1.9). ORs were similar for specific affected sutures, with the exception of multiple affected sutures, for which the OR was 3.0 (95% CI 1.3, 6.9) (Table I).

Relative to control mothers who did not report thyroid disease, control mothers who did report thyroid disease were more likely to be older, be non-Hispanic white, report fertility medications or procedures, have had a previous miscarriage, have gestational diabetes, and take anti-depressants or iron-only supplements, and less likely to smoke, based on $P<0.05$ (Table II). Parity, BMI, hypertension and alcohol consumption were not statistically different ($P\geq0.05$).

We then examined the association of the studied risk factors with craniosynostosis after adjustment for all other factors and excluding women who reported thyroid disease. Maternal younger age (OR 0.7,95% CI 0.6–0.8, for <25 years vs. 25–29), black (OR 0.3, 95% CI 0.2–0.4) or other race-ethnicity (OR 0.6, 95% CI 0.4–0.8), fertility medications or procedures (OR 1.5, 95% CI 1.2–2.0), and alcohol consumption (OR 0.8, 95% CI 0.7–0.9) were associated with risk of craniosynostosis, based on confidence intervals that excluded 1.0 (Table III). Many results were similar regardless of suture type but a few differences from all cases grouped together are noteworthy: sagittal synostosis had the weakest association with fertility treatments; risk of coronal synostosis was not reduced among infants born to mothers with Hispanic and other race-ethnicity; and risk of coronal synostosis was elevated among infants born to mothers with pre-gestational diabetes.

Several results were different for lambdoid cases but should be interpreted with caution given that analyses of this group included only 31 cases (Table III).

DISCUSSION

We examined the association of craniosynostosis with several maternal characteristics that are related to increased risk of thyroid disease, among women who did not report having thyroid disease. After adjustment for all other studied factors, reduced risk of craniosynostosis was observed among babies born to women who were younger, had black or other race-ethnicity, and consumed alcohol, and increased risk was observed among women who took fertility medications or had fertility-related procedures. The directions of the associations of these risk factors with craniosynostosis are consistent with the directions of their associations with thyroid dysfunction. The findings thus lend support to a potential association of craniosynostosis with thyroid dysfunction, even among women who have not been diagnosed with overt thyroid disease.

The associations of craniosynostosis with many of the studied risk factors have been studied previously [Reefhuis et al., 2003; Carmichael et al., 2008; Boulet et al., 2010; Sanchez-Lara et al., 2010; Richardson et al., 2011]. The novelty of the current study is that they have been examined simultaneously in the context of a unifying hypothesis regarding thyroid disease, and they have all been adjusted for confounding by each other. Previous studies have typically focused on one or a few risk factors at a time, adjusted for fewer covariates, included fewer cases, and did not exclude women diagnosed with overt thyroid disease.

Ideally, we would like to examine directly whether maternal thyroid hormone levels or the presence of anti-thyroid antibodies are associated with craniosynostosis. Given that such measurements were not available and would be very difficult to obtain prospectively given the rarity of craniosynostosis, we took the alternative approach of studying risk factors for thyroid dysfunction. This is akin to an approach that has been used to understand the association of estrogen-related exposures with hypospadias and testicular cancer [Carmichael et al., 2007; English et al., 2003]. Initial analyses confirmed that most of the studied maternal characteristics were indeed associated with reported thyroid disease among control mothers. This lends internal validity to our approach.

In our previous analysis of the association of maternal self-reported thyroid disease with craniosynostosis, which was based on births from 1997–2002, the OR was 2.3 (95% CI 1.4, 4.0). In that study, 4.4% of case mothers (19/431) and 1.6% of control mothers (65/4,094) reported having thyroid disease. In the current study, which includes births from 1997–2007, the respective OR and percentages are 1.4 (95% CI 0.9, 1.9), 3.5% and 2.3% of controls. We do not have an explanation for the difference in results using more recent data. Many case reports and series that involve varied scenarios of maternal or newborn thyroid dysfunction have suggested an association with craniosynostosis [Penfold and Simpson, 1975; Johnsonbaugh et al., 1978; Daneman and Howard, 1980; Cove and Johnston, 1985; Leonard et al., 1987; Stevenson and Trent, 1990; Nishihara et al., 2006]. The osteogenic effects of thyroid hormone and experimental data also support the hypothesis [Akita et al., 1994]. Supportive observational epidemiologic data are limited, with the NBDPS offering the

largest set of detailed observational data to date that can be used to address this question. Several other epidemiologic studies have examined the association of maternal thyroid disease with birth defects, but sample sizes have been quite limited [Momotani et al., 1984; Khoury et al., 1989; Wing et al., 1994; Chen et al., 2011; Yoshihara et al., 2012; Andersen et al., 2013; Kallen and Norstedt Wikner, 2014]. A large study of Texas births reported lower thyroxine levels in newborn screening bloodspots among infants with craniosynostosis [Hashmi et al., 2012], a finding that could be expected if the mothers were hyperthyroid during pregnancy.

We acknowledge that thyroid dysfunction and its association with the studied risk factors are complex. For example, alcohol consumption has recently been shown to be protective against development of autoimmune hypo- or hyperthyroidism [Carle et al., 2012b], which supports our observation of reduced risk among women who drank. Another example is smoking. Some studies have suggested that smoking is associated with increased risk of craniosynostosis [Kallen, 1999; Honein and Rasmussen, 2000; Carmichael et al., 2008]. However, a recent report suggested that smoking cessation was associated with increased incidence of hypothyroidism [Carle et al., 2012a]. We would certainly not advocate alcohol consumption or smoking during pregnancy, but this information is potentially useful from an etiologic standpoint and from the perspective of trying to synthesize varied findings. We would also like to note that although the findings do lend support to our hypothesis, mechanisms other than undiagnosed thyroid dysfunction could also explain the observed associations.

Strengths of the current study include its population-based, multi-center design, careful case ascertainment, large size, suture-specific analyses, and simultaneous examination of multiple risk factors. Interviews were conducted with mothers of 71% of eligible cases and 66% of controls. We have no reason to believe that participation was differentially related to the studied risk factors for cases versus controls, but if it was, then selection bias may have affected our results. Similarly, we do not know whether mothers' recall of any risk factors was related to case or control status, but if it was, then recall bias could have affected our results.

This study's findings provide support for the hypothesis that risk factors associated with thyroid dysfunction are also associated with risk of craniosynostosis. Improving our understanding of the potential association between maternal thyroid function and craniosynostosis among offspring is important, given that thyroid disease is common, under-diagnosed and potentially modifiable.

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TABLE I

Association of Maternal Thyroid Disease With Craniosynostosis, National Birth Defects Prevention Study, 1997–2007

Affected suture(s)	No. cases with and without thyroid disease*	AOR (95% CI), adjusted for maternal age**
Any	37/1030	1.4 (0.9, 1.9)
Sagittal	19/547	1.3 (0.8, 2.1)
Metopic	6/188	1.3 (0.6, 3.0)
Coronal	6/181	1.2 (0.5, 2.9)
Lambdoidal	0/32	—
Multiple	6/79	3.0 (1.3, 6.9)

* The sum of the two numbers in the column equals the total number of cases; eg, 37 + 1030 = 1067 cases with any affected suture. Number of controls with and without thyroid disease was 191 and 8303, respectively.

** Adjusted for maternal age as <25, 25–29, 30–34, 35+ years.

TABLE II

Association of Maternal Characteristics With Thyroid Disease Among Control Mothers

	Percent, among mothers with thyroid disease (n = 191)*	Percent, among mothers without thyroid disease (n = 8,303)*	*P*-value
Age (years)			<0.001
<25	11	34	
25–29	29	27	
30–34	34	25	
35 or older	27	14	
Race-ethnicity			<0.001
Non-Hispanic white	73	58	
Non-Hispanic black	4	11	
Hispanic	14	23	
Other	8	8	
Parity (previous live births)			
0	33	40	0.132
1	37	33	
2 or more	30	27	
Pre-pregnancy body mass index**			
Underweight (<18.5 kg/m^2)	3	5	0.066
Normal weight (18.5–24.9 kg/m^2)	49	53	
Overweight (25.0–29.9 kg/m^2)	25	22	
Obesity (30–39.9 kg/m^2)	20	14	
Extreme obesity (40 or more kg/m^2)	3	2	
Fertility medications or procedures	12	4	<0.001
Previous miscarriage			
None	68	78	0.005
1	25	16	
2 or more	7	6	
Diabetes			
None	87	93	0.037
Pre-gestational	1	1	
Gestational	11	6	
Hypertension before or during pregnancy	12	13	0.689
Took anti-depressants (from 3 months before or during pregnancy)	7	4	0.047
Took iron-only supplement			
None	77	72	0.029
Began in 1st trimester	7	13	
Began in 2nd trimester	9	11	
Began in 3rd trimester	6	4	
Smoked (1st trimester)	9	16	0.016
Alcohol consumption (1st trimester)	25	22	0.245

*Column percents do not add to 100% due to missing data.

TABLE III

Association of Maternal Characteristics With Risk of Craniosynostosis, Overall and by Affected Suture(s), Among Mothers Who Did Not Have Thyroid Disease

	Adjusted Odds Ratio (95% CI)*					
	All cases (n = 962)	**Sagittal (n = 513)**	**Metopic (n = 174)**	**Coronal (n = 169)**	**Lambdoidal (n = 31)**	**Multiple suture (n = 72)**
Age (years)						
<25	**0.7 (0.6, 0.9)**	**0.6 (0.5, 0.8)**	0.9 (0.6, 1.3)	0.7 (0.5, 1.2)	0.4 (0.1, 1.2)	1.0 (0.5, 1.9)
25–29	Ref	Ref	Ref	Ref	Ref	Ref
30–34	1.1 (0.9, 1.4)	1.0 (0.8, 1.2)	1.2 (0.8, 1.7)	**1.9 (1.3, 2.8)**	1.3 (0.5, 3.5)	0.8 (0.4, 1.5)
35 or older	1.2 (1.0, 1.5)	1.2 (0.9, 1.5)	1.0 (0.6, 1.7)	1.2 (0.7, 2.1)	2.5 (0.9, 6.9)	1.6 (0.8, 3.1)
Race-ethnicity						
Non-Hispanic white	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic black	**0.3 (0.2, 0.4)**	**0.2 (0.1, 0.4)**	0.6 (0.3, 1.1)	**0.3 (0.1, 0.7)**	–	**0.1 (0.01, 0.7)**
Hispanic	0.8 (0.7, 1.0)	**0.6 (0.4, 0.7)**	0.8 (0.5, 1.2)	1.5 (1.0, 2.2)	**3.4 (1.5, 7.9)**	0.7 (0.4, 1.4)
Other	**0.6 (0.4, 0.8)**	**0.4 (0.3, 0.7)**	0.5 (0.2, 1.0)	1.3 (0.7, 2.2)	0.6 (0.1, 5.0)	0.2 (0.02, 1.1)
Parity (previous live births)						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.1 (1.0, 1.3)	1.2 (1.0, 1.5)	0.9 (0.6, 1.2)	1.1 (0.8, 1.6)	0.7 (0.3, 1.6)	1.3 (0.7, 2.3)
2 or more	1.0 (0.8, 1.2)	1.2 (0.9, 1.5)	0.7 (0.4, 1.0)	1.0 (0.6, 1.5)	**0.2 (0.1, 0.7)**	1.2 (0.6, 2.3)
Pre-pregnancy body mass index						
Underweight (<18.5 kg/m^2)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)	0.8 (0.4, 1.9)	0.9 (0.4, 2.0)	0.7 (0.1, 5.0)	1.9 (0.8, 4.6)
Normal weight (18.5–24.9 kg/m^2)	Ref	Ref	Ref	Ref	Ref	Ref
Overweight (25.0–29.9 kg/m^2)	1.1 (1.0, 1.3)	1.1 (0.9, 1.4)	1.5 (1.0, 2.2)	0.9 (0.6, 1.4)	1.0 (0.4, 2.5)	1.2 (0.7, 2.1)
Obesity (30–39.9 kg/m^2)	1.2 (1.0, 1.5)	1.2 (0.9, 1.5)	1.5 (1.0, 2.3)	1.3 (0.8, 1.9)	1.3 (0.5, 3.5)	1.0 (0.5, 2.1)
Extreme obesity (40 or more kg/m^2)	1.2 (0.7, 1.8)	1.0 (0.5, 1.9)	1.9 (0.8, 4.5)	1.8 (0.8, 4.0)	–	–
Fertility medications or procedures	**1.5 (1.2, 2.0)**	1.2 (0.8, 1.7)	**2.3 (1.4, 3.7)**	**1.7 (1.0, 3.0)**	1.6 (0.5, 5.6)	1.3 (0.5, 3.3)
Previous miscarriage						
None	Ref	Ref	Ref	Ref	Ref	Ref
1	1.1 (0.9, 1.3)	1.0 (0.8, 1.3)	1.4 (1.0, 2.0)	1.0 (0.7, 1.5)	**2.3 (1.1, 5.0)**	0.7 (0.4, 1.5)
2 or more	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)	1.3 (0.7, 2.4)	0.8 (0.4, 1.5)	0.6 (0.1, 4.7)	0.8 (0.3, 2.2)

	Adjusted Odds Ratio (95% CI)*					
	All cases (n = 962)	**Sagittal (n = 513)**	**Metopic (n = 174)**	**Coronal (n = 169)**	**Lambdoidal (n = 31)**	**Multiple suture (n = 72)**
Diabetes						
None	Ref	Ref	Ref	Ref	Ref	Ref
Pre-gestational	1.2 (0.5, 2.5)	0.8 (0.3, 2.7)	0.8 (0.1, 6.1)	**3.4 (1.2, 10.0)**	–	–
Gestational	1.3 (1.0, 1.6)	1.3 (1.0, 1.9)	0.8 (0.4, 1.6)	1.4 (0.9, 2.4)	1.7 (0.5, 5.8)	1.7 (0.8, 3.9)
Hypertension (before or during pregnancy)	1.1 (0.9, 1.3)	1.1 (0.9, 1.5)	0.8 (0.5, 1.3)	1.2 (0.8, 1.8)	0.7 (0.2, 2.3)	1.1 (0.5, 2.1)
Took anti-depressants (from 3 months before or during pregnancy)	1.3 (1.0, 1.8)	1.4 (1.0, 2.0)	1.2 (0.6, 2.4)	1.2 (0.6, 2.4)	2.4 (0.7, 8.3)	1.2 (0.4, 3.3)
Took iron supplements						
None	Ref	Ref	Ref	Ref	Ref	Ref
Began in 1st trimester	1.1 (0.9, 1.3)	1.0 (0.7, 1.3)	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)	1.5 (0.6, 3.7)	1.0 (0.5, 2.1)
Began in 2nd trimester	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)	0.7 (0.4, 1.2)	0.8 (0.4, 1.4)	–	0.8 (0.3, 1.8)
Began in 3rd trimester	0.8 (0.5, 1.2)	1.0 (0.6, 1.5)	0.7 (0.3, 1.8)	0.8 (0.3, 1.9)	0.7 (0.1, 5.5)	–
Smoking (1st trimester)	1.0 (0.8, 1.2)	1.0 (0.7, 1.3)	0.8 (0.5, 1.3)	1.2 (0.8, 1.8)	**3.2 (1.4, 7.3)**	0.6 (0.3, 1.3)
Alcohol consumption (1st trimester)	**0.8 (0.7, 0.9)**	0.8 (0.6, 1.0)	0.8 (0.6, 1.2)	0.8 (0.5, 1.1)	1.5 (0.7, 3.2)	0.8 (0.4, 1.4)

*All odds ratios are adjusted for all other variables in the table. All models included 7,417 controls. Cases (n = 68 of 1,030) and controls (n = 886 of 8,303) with missing data on any covariates were excluded. Bold font indicates 95 % CI excluding 1.0 before rounding into one decimal place.