Advanced parental age: Is it contributing to an increased incidence of non-syndromic craniosynostosis? A review of case-control studies

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Abstract

Background: Craniosynostosis (CS) is a congenital birth defect characterized by the premature fusion of one or several calvarial suture(s). CS could lead to serious complications, such as intracranial hypertension and neurodevelopmental impairment. There is an increasing trend in the prevalence of CS – 75% of which are of non-syndromic type (NSCS). In parallel, there is a steady rise in the average maternal age. The goal of this paper was to review the literature to clearly identify any associations between parental age and NSCS. This review was performed and reported in compliance with PRISMA guidelines.

Methods: The PUBMED and EMBASE databases were systematically searched, and all studies that observed the relationship between maternal and/ or paternal age on NSCS were included. The articles were then assessed for methodological quality using the Newcastle–Ottawa Scale (NOS). The effect of advanced maternal and/ or paternal age on the incidence of NSCS was identified by the prevalence ratios reported at a confidence interval of 95%.

Results: Six retrospective case-control studies, reporting on a total of 3267 cases of NSCS were included in this review. While there were some inconsistencies in the findings of the different studies, the majority reported a positive correlation between advanced maternal and/ or paternal age and an increased incidence of NSCS.

Conclusion: This review identified an association between advanced parental age and an increased incidence of NSCS.

Keywords: Craniosynostoses; advanced parental age; advanced maternal age; advanced paternal age

Introduction

The last few decades have witnessed a consistent increase in average maternal age at first birth.[1] Previous data from the United States show that the birth rates for females aged 30 and above have increased since the 1990s, with rates for females aged over 40 years old rising continuously since 1985. While there is no direct causation to explain the effect, both advanced maternal and paternal ages have been associated with a potential decrease in the health and well-being of offspring.[2] In regards to congenital malformations, parental age is a known risk factor.[3] Although there is a general consensus that advanced maternal age (AMA) is associated with a higher incidence of congenital abnormalities, some studies demonstrate a protective effect of AMA, specifically in the absence of aneuploidy.[4] The relationship becomes more ambiguous with regards to paternal age mainly due to the fact that it is significantly less studied in the literature.[3]

Craniosynostosis (CS) is defined as the premature fusion of a single or multiple cranial vault suture(s).[5] While not all CS cases are operative, early diagnosis is important to determine prognosis and treatment plans since it could lead to serious complications such as intracranial hypertension and neurodevelopmental impairment.[6] The prevalence of CS is approximately 1 in 2500 live births, and there is evidence of an increasing trend.[7] Cases of CS are present in all racial groups, and though the exact causes are unknown, both genetic and non-genetic factors are believed to influence the development of this condition.[8] While non-syndromic craniosynostosis (NSCS) comprises the vast majority of CS cases (75%), CS associated syndromes are significantly more studied and therefore better understood in terms of pathophysiology and prognosis.[9] NSCS usually occurs sporadically and arises from unaffected parents. Several risk factors have been associated with NSCS, such as being of Caucasian descent, maternal thyroid

disease, and smoking during pregnancy.[10-12] While some studies suggest a relationship between AMA and NSCS, others do not support it as being an independent risk factor.[13] The same is true for paternal age, where no relationship has been established.[14]

While many studies have established clear genetic associations and causative mutations in CS associated syndromes, NSCS is much less studied and the pathogenesis of the condition is not well understood.[9] The goal of this paper was to systematically review the literature to clearly identify any associations between parental age and NSCS. The results of this review will disseminate important epidemiological information and highlight any potential association between parental age and NCSC. This can be used to inform targeted interventions to decrease its incidence and morbidity through, for example, adequate parental counseling, earlier diagnosis, and treatment, as well as encourage further research on the etiology of the condition, such as potential point mutations in sperm DNA of older males.[15]

Methods

The PUBMED and EMBASE databases were systematically searched initially on May 13, 2019, then again prior to publishing on October 17, 2020 for relevant articles related to parental age and the incidence of NSCS. The search strategy included both keywords and MeSH terms in order to capture all relevant studies. The specific search strategy used for PUBMED was the following: (((“maternal age” OR “paternal age” OR “parental age” OR “age”) OR “paternal age”[Mesh]) OR “maternal age”[Mesh]) AND (“craniosynostosis”)

This systematic review was performed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[16] Two authors independently reviewed all the results search entries for inclusion and exclusion criteria. Any discrepancies between the authors were settled by a third researcher. Inclusion criteria consisted

of case-control studies that described the relationship between maternal and/ or paternal age on NSCS. Exclusion criteria consisted of papers that exclusively discussed syndromic conditions, such as Apert, Pfeiffer, Courzon, Meunke, and Beare-Stevenson Cutis Gyrata syndrome. However, studies of a heterogeneous population that did a separate analysis of their non-syndromic subjects were included. Studies that solely investigated the effect of other risk factors, such as maternal smoking, maternal exposure to second-hand smoking, maternal thyroid disease, fertility treatments, maternofetal trauma, maternal SSRI intake, and maternal occupation on the incidence of NSCS were all excluded as well. Finally, animal and cadaver studies were excluded.

All included articles went through methodological quality assessment for potential risk of bias using the Newcastle–Ottawa Scale (NOS) for case-control studies.[17] The selected articles were then analyzed, and the following data were extracted: study design, year of publication, country of study, period of study, sample size, sample population distribution of NSCS sub-types, mean maternal age, and mean paternal age. Data on the influence of maternal and/ or paternal age on the incidence of NSCS, as well as the influence of either parental age on individual CS sub-types when available was identified by the prevalence ratios reported in the studies. Finally, the controlled cofounding covariables were noted when mentioned in the papers.

Results

The search on PUBMED and EMBASE on October 17, 2020 yielded 1174 papers. After assessing titles and abstracts for inclusion and exclusion criteria, 40 studies fulfilled the criteria and were fully read, yielding a final six articles to be included in this review. (Figure 1) Eleven papers were excluded because they did not assess the effect of parental age on NSCS. Eleven papers studied syndromic CS. All six included articles were retrospective case-control studies, and four of which had a “good” quality rating, as per NOS assessment. (Table 1)

The publishing year of the studies ranged from 1999 to 2015, including cases of infants born between 1968 to 2008. There was a wide representation in terms of population of study: USA (3), Australia (2), and Denmark (1). With a total of 3267 cases of NSCS included in this review, the smallest study included 170 cases, and the largest included 997 cases. Of the six retrospective case-control studies, one studied the effect of both paternal and maternal age,[18] four solely examined the effect of maternal age,[15,19-21,] and one exclusively investigated paternal age.[15] (Table 2)

Four of the five case control studies that investigated the effect of maternal age found a positive effect of AMA on the incidence of NSCS.[19,20,22,23] Boulet *et al.* found that maternal age between 35 and 44 is associated with an increased incidence of NSCS: OR 2.20 (95% CI 1.63, 2.99). Their sub-analysis further showed that the sagittal and metopic sub-types were the ones most impacted by AMA (sagittal: OR 2.32 (95% CI 1.48, 3.63), metopic: OR 2.27 (95% CI 1.16, 4.45), lambdoid: OR 2.08 (95% CI 1.04, 4.17), coronal: OR 1.98 (95% CI 0.93, 4.24)).[23] Similarly, Lee *et al.* associated maternal age between 30 and 39 with a small but significant increase in the incidence of NSCS, OR 1.26 (95% CI 1.04, 1.53), while maternal age over 40 to be associated with a larger increase, OR 1.92 (95% CI 1.17, 3.15).[20] Lee *et al.* further reports that AMA had the strongest effect on the sagittal and metopic sub-types (sagittal: OR 2.01 (95% CI 0.97, 4.14), metopic: OR 3.00 (95% CI 1.18, 7.63), coronal: OR 1.17 (95% CI 0.28, 4.84)).[20] Reefhuis *et al*. showed that maternal age between 35 and 40 was associated with an increased risk of NSCS, OR 1.65 (95% CI 1.18, 2.30), but did not report on the different sub-types of NSCS cases included in the study.[22] Finally, Gill *et al*. found that not only is AMA associated with an increased incidence of NSCS (35-39: OR 1.3 (95% CI 1.1, 1.6), >40: OR 1.6 (95% CI

1.1, 2.4)), but that young maternal age (<20) can be protective: OR 0.6 (95% CI 0.4, 0.8).[19] (Table 3)

On the other hand, one smaller retrospective study published in 1999 in Australia found no statistically significant effect of maternal age on the incidence of this congenital condition.[18] Singer *et al*. specified their study population to be composed of the following distribution: 41.2% sagittal, 21.8% lambdoid,15.9% coronal and 7.0% multi-sutural, and further sub-analyzed the AMA effect (sagittal: OR 2.34 (95% CI 0.91, 5.63), coronal: OR 1.40 (95% CI 0.28, 6.89), lambdoid: OR 1.20 (95% CI 0.33, 4.41)).[18] (Table 3)

The two studies that investigated the effect of paternal age found a positive effect of increased age on the incidence of NSCS.[15,18] After exclusion of the known autosomal dominant syndromes, Singer *et al.* concluded that fathers aged 40 years and over were almost three times as likely to have a child with CS: OR 2.72 (95% CI 1.40, 5.28).[18] They further sub-analyzed the paternal effect on sub-types (sagittal: OR 2.11 (95% CI 0.89, 5.00), coronal: OR 2.03 (95% CI 0.39, 10.61) lambdoid: OR 5.09 (95% CI 1.45, 17.85)).[18] In another study, a statistically significant effect of paternal age was only demonstrated in fathers over 50 years old: OR 1.36 (95% CI 0.71, 2.59).[15]

Discussion

The results of this review demonstrate that AMA is associated with an increased incidence of NSCS, as reported by four of the five articles that studied the relationship.[19,20,22,23] Similarly, advanced paternal age was shown to positively correlate with an increased incidence of NSCS by both articles that studied the effect.[15,18] To the authors' knowledge, there are no systematic literature reviews that have previously summarized the effect of parental age on the incidence of congenital NSCS.

Though the majority of the included papers in this review found a statistically significant effect of AMA on the incidence of NSCS, the inconsistent epidemiologic outcomes can be potentially explained by the different patient population characteristics and distribution of NSCS sub-types included in each study. For instance, both Boulet *et al.* and Lee *et al*. which had similar sub-type distribution (majority sagittal and metopic) demonstrated a strong correlation between AMA and an increased incidence of NSCS.[20,23] On the other hand, Singer *et al.,* who demonstrated a small, though statistically insignificant association between maternal age and the incidence of NSCS, had a different sample composition, mainly composed of sagittal and lambdoid NSCS.[18] Furthermore, both Boulet *et al.* and Lee *et al.* showed a stronger correlation between AMA and particular sub-types of NSCS: both studies showed that the sagittal and metopic sub-types increase the most with AMA. Therefore, the fact that AMA affects particular sub-types of NSCS, while having no effect on others can potentially explain why some studies showed no effect of AMA on the incidence of NSCS.

Furthermore, the retrospective studies analyzed populations of different time periods; Singer *et al.* had the oldest population between 1980 and 1994, and the largest proportion of lambdoid CS sub-type. This is potentially because of old diagnostic modalities that could not differentiate between true lambdoid synostosis and plagiocephaly.[24] Indeed, Boulet *et al.* showed a significant decrease in the incidence, or diagnosis of lambdoid CS between 1989 and 2003.[23] Furthermore, this decrease is coupled with a statistically significant increase in incidence of metopic CS between 1982 and 2008,[20] as well as between 1975 and 2004, as demonstrated by Selber *et al*.[25] This increase in metopic synostosis is thought to be either due to better diagnostic modalities or novel environmental risk factors.[25,26]

Moreover, the presence of confounding factors may mask an existing association or falsely point to one when an association fails to exist. For instance, previous studies have identified multiple factors that increase the risk of NSCS, including maternal race, maternal residence at high altitudes, male infant sex, maternal smoking, certain paternal occupations (ex. agriculture, forestry, mechanics, repairman) and fertility treatments.[23,25] Although all of the studies report controlling for particular risk factors, there were notable variations in the ones each paper addressed. (Table 2)

The results of this review raise an important question regarding the effect of AMA on different maternal genetic pools. All three studies conducted in North America showed a significant association between AMA and increased incidence of NSCS. The two studies conducted in Australia showed mixed results; one demonstrated similar findings to the North American studies, while the other found no correlation between the specified factors. The authors believe a future cross-sectional study observing the effect of AMA on NSCS in various populations (ethnic/ racial groups) across several regions (countries), while controlling for other confounding variables known to impact the incidence of NSCS is warranted and can help shed light into this topic.

The main limitation of this review is the lack of quantitative analysis. The heterogeneity of the studies' methods, including statistical analyses conducted render a meta-analysis not viable. To further elaborate on methodological differences, there was significant variability in the confounding variables accounted for in the statistical analyses of the studies – in fact, some studies did not control for any risk factors. Similar wide variability was noted for the stratification of maternal and paternal ages in the studies - particularly in studies that were conducted in earlier years. Although AMA is now commonly defined as pregnant at age 35 and

older,[27] maternal age groups used in the included studies varied between, <20, 20-24, 25-29, 30-35, 35+, 35-40, and 40+. Moreover, this review demonstrates that AMA could potentially affect certain sub-types of NSCS compared to others, therefore, future studies should stratify their analysis bases on the sub-types. Finally, although all the studies that investigated the effect of parental age showed an effect of advanced age on the incidence of NSCS, a definite association is limited by the small number of total (6) and high-quality (4) papers examining this relationship – especially in regards to the effect of paternal age (2).

Over the past two decades, there have been several studies that investigated and identified some genetic markers for CS. Mutations in the fibroblast growth factor receptors (*FGFR*) are believed to cause an abnormality of osteoprogenitor cells within cranial sutures.[28] In 1998, Gripp *et al.* indeed found a single gene mutation of *FGFR3 (Pro250Arg)* to be associated with non-syndromic coronal CS.[29] Another study recommended *FGFR3-Pro250Arg* testing for 1st line molecular genetic diagnosis for both non-syndromic unicoronal and bicoronal CS.[30] Most recently in 2017, a review on genetic advances in CS concluded that genetic causes of NSCS are still unknown; however, testing patients with coronal and complex NSCS for *FGFR1*, *FGFR2*, *FGFR3*, *TWIST1*, *TCF12,* and *ERF* may be warranted.[26] In cases that are clinically ambiguous, genetic analysis may be beneficial, as it may lead to early diagnosis with less radiation-intensive imaging techniques.

Other diagnostic and screening modalities for CS include ultrasound (US), computer tomography (CT), and magnetic resonance imaging (MRI). This review raises the question of whether there is sufficient compelling data to provide meaningful information for family counseling and screening programs. Screening may not only be carried prenatally, but also in the first days or weeks of life. In the case of CS, the increased incidence observed in mothers over

the age of 35 and fathers over the age of 40 may be compelling ground for further investigations on the impact of screening on improving outcomes for newborns with CS. In certain cases, diagnosis can be made by prenatal fetal US through indirect signs, such as abnormal cephalic index (CI), cranial shape, and/or face morphology.[31] Moreover, MRI imaging could be used to show skull deformities and thickening of the calvarium.[32,33] However, reports on prenatal diagnosis of CS are rare in the literature. Alternatively, babies born to mothers over 35 and/ or fathers over 40 years old may be followed more closely or undergo formal screening during their infancy in order to ensure that a diagnosis of CS is not missed, given the serious possible sequelae of the condition, as well as the benefit of a non-invasive surgical treatment in babies under 6 months of age.

Postnatal diagnosis of CS is usually done by clinical examination of the abnormal skull. While post-natal CT scans can help in diagnosing NSCS, its use as a screening tool is not common practice. The benefits of diagnosing and correcting CS in a timely manner have to be weighed against the risk of exposure to radiation. A 2017 study by Montoya *et al.*, assessed the potential for radiation dose reduction by using simulated CT images with 25%, 10%, or 2% of the initially applied radiation dose.[33] The study was able to show that radiation dosages can be reduced by 75%-90% without compromising observer performance when evaluating pediatric CT scans for CS. The impact of such findings becomes particularly important in cases of multi-sutural CS, where CT scans may be indicated for diagnosis, treatment planning, and follow-up - exposing the child to multiple rounds of radiation. On the other hand, the use of US in adjunction to clinical evaluation has been shown to be a reliable and preferred screening tool for patients with CS, as it can identify several of its unique features.[34] In a 2017 retrospective review by Hall *et al.*, 52 patients with a mean age of 4.6 months old were evaluated for CS by both sonography

and CT scanning. The results of the study showed an US sensitivity of 100%, a specificity of 100%, and negative predictive value of 100% when used to screen for CS. The study concluded that US can be used as a reliable screening tool and has potential use in ruling-out CS in patients with an abnormal head shape.[32] Finally, the use of MRI in screening or diagnosis of CS is not common and is frequently used only in conjunction with US. MRI may serve to identify brain abnormalities, but it has limited ability in identifying cranial sutures.

Conclusion

NSCS comprises the majority of the CS cases worldwide. However, the epidemiological outcomes and risk factors associated with the non-syndromic cases are significantly less studied. This review summarizes the effect of both maternal and paternal age on the incidence of NSCS. While there are some inconsistencies in the results of different papers, there is compelling evidence suggesting an association between both advanced maternal and paternal age and increased incidence of NSCS. Understanding risk factors such as paternal age is necessary for the understanding of the pathogenesis of the condition, as well as proper prenatal care including genetic counseling, screening, and prevention.

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		Boulet et al. 2008	*Gill et al. 2012*	*Lee et al. 2012*	*Urhoj et al. 2015*	*Singer et al. 1999*	*Reefhuis et al. 2004*
Selection	1) Is the case definition adequate? a) yes, with independent validation* b) yes, eg record linkage or based on self-report c) no description	A*	A*	B	B	A*	B
	2) Representativeness of the cases a) consecutive or obviously representative series of cases* b) potential for selection bias or not stated	A*	A*	A*	A*	A*	A*
	3) Selection of controls a) community controls* b) hospital controls c) no description	A*	A*	A*	A*	A*	A*
	4) Definition of controls a) no history of disease (endpoint)* b) no description of source	B	A*	B	A*	A*	A*
Comparab	Comparability of cases and controls on the basis of the design or analysis a) study controls for parental demographics (maternal age,	A*B*	A*	B*	A*B*	B*	A*

	race, paternal age, race, parental education), period born* b) study controls for any additional factors ex. syndromic defects*						
Exposure	1) Ascertainment of exposure a) secure record, eg. surgical record* b) structured interview where blind case/control* c) interview not blinded to case/control status d) written self-report or medical record only e) no description	A*	C	A*	A*	A*	A*
	2) Same method of ascertainment for cases and controls a) yes* b) no	B	A*	B	A*	A*	A*
	3) Non-response rate a) same rate for both groups* b) non-respondents described c) rate different and no designation	C	A*	C	C	C	C
	Total Number of Stars	6	7	4	7	6	6
	Quality Rating According to Guideline[a]	*Poor*	*Good*	*Poor*	*Good*	*Good*	*Good*

Table 1. Newcastle-Ottawa Scale assessment of non-randomized case-control studies

**=one star*

a. Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality - AHRQ - standards (good, fair, and poor): ***Good quality:*** *3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Exposure domain;* ***Fair quality:*** *2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Exposure domain;* ***Poor quality****: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Exposure domain*

Article	Country, Period of Study	Sample Size (NSCS/ control)	Controlled Confounding Covariables	Maternal Age Stratification	Prevalence Ratio (OR (95% CI))	Influence of Young Maternal Age	Influence of Advanced Maternal Age	Paternal Age Stratification	Prevalence Ratio (OR (95% CI))	Influence of Young Paternal Age	Influence of Advanced Paternal Age
Boulet *et al.* 2008	USA, 1989-2003	216/N/A	None	15-19 20-34 35-44	0.29 (0.13, 0.66) 1 2.20 (1.63, 2.99)*	None	Positive	N/A	N/A	N/A	N/A
Gill *et al.* 2012	USA, 1997-2007	966/8169	Maternal race, education, BMI, periconceptional folic acid, gravidity, smoking, parental age difference	<20 20-24 25-29 30-34 35-39 40+	0.6 (0.4, 0.8)* 0.8 (0.6, 1.0) 1 1.2 (1.0, 1.4) 1.3 (1.1, 1.6) 1.6 (1.1, 2.4)*	Negative	Positive	N/A	N/A	N/A	N/A
Lee *et al.* 2012	Australia, 1982-2008	522/N/A	None	<20 20-29 30-39 40_ 40+	0.64 (0.33, 1.25) 1 1.26 (1.04, 1.53)* 1.92 (1.17, 3.15)*	None	Positive	N/A	N/A	N/A	N/A
Reefhuis *et al.* 2004	USA, 1980-1994	396/1050616	Parity, maternal race, infant sex, year of birth	14-19 20-24 25-29 30-34 35-40	N/A N/A 1 N/A 1.65 (1.18, 2.30)*	None	Positive	N/A	N/A	N/A	N/A
Singer *et al.* 1999	Australia, 1980-1994	170/522	None	<20 20-24 25-29 30-34 35+	0.54 (0.23, 1.26) 0.89 (0.56, 1.42) 1 1.13 (0.73, 1.76) 1.80 (0.96, 3.41)	None	None	<25 25-29 30-34 35-39 40+	1.02 (0.57, 1.82) 1.21 (0.76, 1.91) 1 1.50 (0.85, 2.66) 2.72 (1.40, 5.28)*	None	Positive
Urhoj *et al.* 2015	Denmark, 1978-2004	997/1605885	Maternal age, year of birth, parental education, parental ethnicity	N/A	N/A	N/A	N/A	<25 25-29 30-34 35-39 40-44 45- 49	1.03 (0.78, 1.35) 1.02 (0.86, 1.21) 1 1.11 (0.92, 1.34) 1.06 (0.79, 1.43) 1.27 (0.80, 2.01)	None	Positive

	50+	1.36 (0.71, 2.59)*

Table 2. Country of Study, period of study, sample size, controlled confounding variables, and influence of paternal age on incidence of NSCS as shown in the case-control studies included in the review

*Statistically significant

Article	Sample Population Distribution of NSCS Sub-types	Advanced Maternal Age	Prevalence Ratio (OR (95% CI))	Advanced Paternal Age	Prevalence Ratio (OR (95% CI))
Boulet *et al.* 2008	39% sagittal (n=100) 19% metopic (n=48) 17% lambdoid (n=43) 17% coronal (n=44) 8% multi-sutural (n=20)	35-44	sagittal: 2.32 (1.48, 3.63)* metopic: 2.27 (1.16, 4.45)* lambdoid: 2.08 (1.04, 4.17)* coronal: 1.98 (0.93, 4.24) N/A	N/A	N/A
Lee *et al.* 2012	47% sagittal (n=246) 21.5% metopic (n=112) 17.1% coronal (n=89) 1.3% lambdoid (n=7) 13% multi-sutural (n=68)	40+	sagittal: 2.01 (0.97, 4.14)* metopic: 3.00 (1.18, 7.63)* coronal: 1.17 (0.28, 4.84) N/A multi-sutural: 1.44 (0.34, 6.02)	N/A	N/A
Singer *et al.* 1999	41.2% sagittal (n=70) 21.8% lambdoid (n=37) 15.9% coronal (n=27) 2.9% metopic (n=5) 7.0% multi-sutural (n=12	35+	sagittal: 2.34 (0.91, 5.63) lambdoid: 1.20 (0.33, 4.41) coronal: 1.40 (0.28, 6.89) N/A	40+	sagittal: 2.11 (0.89, 5.00)* lambdoid: 5.09 (1.45, 17.85)* coronal: 2.03 (0.39, 10.61)* N/A

Table 3. Sample population distribution and sub-analysis of the influence of advanced parental age on incidence of NSCS sub-types

*Statistically significant