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High risk factors for craniosynostosis during pregnancy: A case-control study

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ABSTRACT

Background: Craniosynostosis is a birth defect involving premature cranial sutures' fusion with an increasing prevalence and unknown underlying causes in nearly 80% of cases. The current study investigates a series of high-risk factors associated with a non-syndromic craniosynostosis.
Methods: Ninety-seven (97) children were included in the retrospective case-control study, 62 controls and 35 with craniosynostosis. A questionnaire with 143 questions was used in face-to-face interviews. After univariate analyses, stepwise multivariate logistic regression analysis was implemented.
Results: In craniosynostosis group, 3 out of 4 were male subjects and 2 out of 3 born with caesarian section. History for central nervous system abnormalities in their younger siblings, low birth weight, extended use of mobile phone from the parents and medications' use differed significantly between craniosynostosis and control group. After adjustment for all factors, only maternal medication use (aOR 6,1 [2.1 – 19], CI 95%) and oral progesterone intake (aOR 4 [1.2 – 14], CI 95%) were significantly associated with an increased risk in craniosynostosis group.
Conclusion: The maternal medications' use and particular oral progesterone intake is associated with an increased risk for non-syndromic craniosynostosis. However, due to the study's limitations, further research is warranted.

1. Introduction

Craniosynostosis (CS) is a birth defect, in which cranial sutures fuse prematurely, commonly disturbing brain growth [1]. CS prevalence has risen over the last decades, currently being between 1 in 2000 to 2500 live births [2,3]. The commonest single-suture synostosis form is the sagittal (40–60%), however changes in CS subtypes' demographics are taking place with a marked increase in the metopic form (20–50%) [4]. Apart from syndromic CS associated with specific genetic mutations and accounting for 1 in 5 cases, no specific known etiology exists for the isolated cases and several predisposing factors are considered to play a role. Various studies have demonstrated an association of CS with biomechanical, environmental, and hormonal variables [1,5]. The current study investigates the possible association of all-known factors with an increased risk of CS occurrence.

2. Materials and methods

2.1. Data sources

The current case-control study on CS children was admitted in the Neurosurgery Department of Agia Sophia, Athens Children's Hospital in a 5-year continuous period. This Pediatric Neurosurgical Clinic is responsible for more than 70% of neurosurgical pediatric operations in Greece in children of 0–14 years of age. The Clinic records were used after the Ethics Committee's special permission. Non-syndromic CS patients were identified based on clinical phenotype and the absence of common coexisting features and syndrome-specific functional issues, including face abnormalities, such as exophthalmos, midface hypoplasia, and limb anomalies. The patients' parents were contacted and asked for their participation after written informed consent. The sample consisted of 97 children, 35 in the CS (group A) and 62 in the control group

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(group B). The majority of subjects in control (62.9%) and CS (74.3%) group were males. Data regarding the patients' hospitalization were then extracted.

A questionnaire with a total of 143 questions was used to interview parents in person (Supplementary Materials). The replies contained information on demographics, delivery, prenatal and perinatal history, maternal medical history, medication during pregnancy and possible high-risk behaviors or habits, such as smoking or alcohol intake, diet, occupation, exposure to chemicals, etc. The same information was included about the paternal medical history and behavior during pregnancy, as well as details on birth characteristics. Interviews were conducted in the hospital by the author SP. Replies were extracted in an Excel worksheet and paired with the data retrieved from their hospitalization.

The *control group* was randomly selected from children that were hospitalized for brain or head injuries and were matched with a 2–1 ratio to the patients' cohort. Based on the frequency of antenatal risk factors in the general population of healthy subjects and with alpha significance level set at 0.05, a required sample of 100 participants was calculated. Therefore, due to the low prevalence of CS, we opted for a 2–1 ratio of controls to cases, to achieve the goal of sufficient number of participants and increase the statistical power to a minimum of 85%. Matching was performed for age (± 1 year) and gender.

2.2. Statistical analysis

Quantitative variables were expressed as mean values ± standard deviation (SD), while categorical variables were expressed as absolute and relative frequencies. For the comparison of proportions, chi-square and Fisher's exact tests were used. Student's t-tests were computed for the comparison of mean values. Stepwise logistic regression analysis (p for entry 0.05, p for removal 0.10) was used to identify possible association between independent factors and the patient group. All variables that showed significant association in the univariate analysis were entered in the multiple logistic regression model and adjusted odds ratios (OR) with a 95% confidence interval (95% CI) were computed. All reported p-values are two-tailed. Statistical significance was set at $p < 0.05$ and analyses were conducted using SPSS statistical software (version 19.0).

3. Results

No significant differences were identified between patients and controls, as far as maternal age during pregnancy, gender and place of birth were concerned. Information about parent's residence in urban versus rural areas, near high voltage lines, chemical processing facilities or increased altitude before and during pregnancy did not differ significantly (Table 1).

Information regarding labor and perinatal outcome is summarized in Table 2. Two out of three CS children (68.6%) were born with cesarean section, while the controls' percentage was significant lower (37.1%, p = 0.006). Birth weight and height in patients' group were significantly lower compared to the controls' group. Type of conception did not differ significantly between patients and controls. CS children had a significantly greater percentage of history for central nervous system (CNS) abnormalities in their younger siblings compared to controls (Table 3).

Environmental factors, expressed through high-risk behavior of parents before and during pregnancy, are summarized in Table 4. In univariate analysis, proportion of mothers that used mobile over than 40 min, on a daily basis, before and during pregnancy was significantly greater in CS compared to control group, as well as the fathers' proportion that used mobile phone before pregnancy. A significantly higher percentage of mothers that were using oral medication (antihistamines, antidepressants, anticonvulsants, thyroxine, and others) during pregnancy (45.7%) compared to controls (14.5%) was identified in CS group. No significant difference was found in mothers' gynecological history and health condition during pregnancy, as well as parental chromosome control between two study groups. As far as mothers' medical treatment is concerned, univariate analysis found that micronized progesterone (Utrogestan®) was prescribed from the obstetrician in a significantly higher frequency to CS group's mothers (34.3%) compared to control group's mothers (11.3%).

The multivariate logistic regression analysis showed that mothers' oral medication intake and specifically that of oral progesterone use

Table 1
Sample characteristics for the control (group A) and craniosynostosis (group B) group.

Sample characteristics	Control group (A) (N = 62)	Craniosynostosis group (B) (N = 35)	p-value
	Mean ± SD	Mean ± SD	
Children age (years)??	3.6 ± 2.7 ??	0.6 ± 0.4 ??	< 0.001+
Mother's age	35.4 ± 4.8	32.4 ± 3.9	< 0.001+
Father's age	38 ± 6.0	36.6 ± 5.7	0.264+
Age during pregnancy	31.4 ± 4.9	31.4 ± 3.9	0.989+
Gender	N (%)	N (%)	
Males	39 (62.9%)	26 (74.3)	0.252‡
Females	23 (37.1%)	9 (25.7)	
Born in Greece	N (%)	N(%)	p-value
No	4 (6.5%)	1 (2.9)	0.651 *
Yes	58 (93.5)	34 (97.1)	

‡Pearson's chi-square test; *Fisher's exact test; +Student's t-test

Table 2
Information regarding birth and perinatal outcome for the control and craniosynostosis group, N = number of subjects.

Information concerning birth and perinatal outcome	Control group (A)	Craniosynostosis group (B)	p-value
	N (%)	N (%)	
Cephalopelvic disproportion during labor			
No	60 (98.4)	34 (97.1)	1.000
Yes	1 (1.6)	1 (2.9)	*
Premature rupture of the amniotic sac			
No	61 (98.4)	34 (97.1)	1.000
Yes	1 (1.6)	1 (2.9)	*
Intrauterine intracerebral - intraventricular hemorrhage			
No	62 (100.0)	35 (100.0)	-* *
Yes	0 (0.0)	0 (0.0)	
Premature labor			
No	61 (98.4)	31 (88.6)	0.055
Yes	1 (1.6)	4 (11.4)	*
Perinatal asphyxia			
No	60 (96.8)	31 (88.6)	0.184
Yes	2 (3.2)	4 (11.4)	*
Labor type			
Cesarean section	23 (37.1)	24 (68.6)	0.003‡
Normal	39 (62.9)	11 (31.4)	
Conception			
Normal	59 (95.2)	34 (97.1)	1.000
Assisted Reproduction	3 (4.8)	1 (2.9)	*
Mean birth weight ± SD (gr)	3254.4 ± 464.1	2954.4 ± 770.2	0.029 +
Low/ Very low birth weight			
No	60 (96.8)	31 (88.6)	0.184
Yes	2 (3.2)	4 (11.4)	*
Mean birth height ± SD (cm)	51.3 ± 2.4	48.7 ± 5.7	0.004 +
Mean head circumference ± SD (cm)	34.1 ± 1.2	33.7 ± 3.2	0.849 +

+Pearson's chi-square test; *Fisher's exact test; +Student's t-test; * *was not computed due to no distribution

Table 3
Family history for central nervous system (CNS) or similar abnormalities for the control grpup (A) and craniosysnostosis group (B).

Family's history		Control group (A)	Craniosynostosis group (B)	p-value
		N (%)	N (%)	
Mother's history for CNS abnormalities	No	61 (98.4)	31 (88.6)	0.055
	Yes	1 (1.6)	4 (11.4)	a
Father's history for CNS abnormalities	No	62 (100.0)	34 (97.1)	0.361
	Yes	0 (0.0)	1 (2.9)	a
Mother's history for similar abnormalities	No	61 (98.4)	32 (91.4)	0.132
	Yes	1 (1.6)	3 (8.6)	a
Father's history for similar abnormalities	No	59 (96.7)	35 (100)	0.532
	Yes	2 (3.3)	0 (0)	a
Mother's history multicystic kidneys	No	61 (98.4)	35 (100)	1.000
	Yes	1 (1.6)	0 (0)	a
Father's history multicystic kidneys	No	62 (100.0)	35 (100)	-b
	Yes	0 (0.0)	0 (0)	
Younger sibling's history for CNS abnormalities	No	62 (100.0)	32 (91.4)	0.044
	Yes	0 (0.0)	3 (8.6)	a
Younger sibling's history for similar abnormalities	No	62 (100.0)	34 (97.1)	0.361
	Yes	0 (0.0)	1 (2.9)	a

[a] Fisher's exact test
[b] was not computed due to no distribution

during pregnancy was significantly correlated with CS. Children whose mother was exposed in medication during pregnancy had an aOR of 6.3 [aOR 2.1–19, CI 95%] for being in CS group as compared to those whose mother did not use any medication. Children whose mother received progesterone during pregnancy had 4 times greater odds [aOR 1.2 – 14, CI 95%] for being in CS group (Table 5).

4. Discussion

The etiology of isolated CS in infants is widely unknown, while several studies have reported various prenatal and perinatal conditions as potential risk factors [1,5]. Moreover, CS prevalence has seemingly increased over the last 30 years without an apparent cause [2–4].

In the present study, the male predominance in CS with a 3:1 ratio was validated over females. Sagittal and metopic CS showed a strong male preponderance, in contrast to coronal CS, in which female cases were more frequent [6,7]. Cesarean section was associated with an increased crude risk of CS; however, it is not clear whether there was a need for a non-planned cesarean section due to anomalies during pregnancy, fetal malpresentation or dystocia that could be indirectly related with CS occurrence.

A crude association was also detected between low-birth weight and height and CS compared to controls. Studies have showed that most birth defects are significantly associated with low-birth weight for a variety of reasons, including intrauterine growth retardation and premature birth [8]. In Sanchez-Lara et al. retrospective study, in which fetal constraint was under investigation as a possible risk factor for CS, prematurity and low-birth weight was significantly associated with CS [9]. Fetal position was not a significant risk factor in the current study either.

The fact that there is increased crude risk of CS with a family history of CNS abnormalities in younger siblings could indicate a kind of genetic predisposition. In syndromic CS, specific gene (FGFR, TWIST and MSX2) mutations have been identified as causes [10,11]. Non-syndromic, isolated CS, however, arises from a multidimensional combination of factors, and it has been proposed that in some subtypes, especially the coronal CS, the disorder could be transmitted genetically, as suggested by proband segregation analysis [7]. Therefore, a positive family history could be considered as a risk factor for coronal suture fusion.

Cell phones, among all wireless devices, emit electromagnetic radiation. While the effects of mobile phones on pregnancy are still being studied, no study has proved a negative effect on fetal development so

Table 4
High risk parental behaviors before and during pregnancy for the control and craniosynostosis group.

High risk parental behaviors before and during pregnancy	Control group (A)	Craniosynostosis group (B)	p-value
Before pregnancy	N (%)	N (%)	
Smoking (father)			
No	24 (38.7)	14 (40.0)	0.901
Yes	38 (61.3)	21 (60.0)	+
Alcohol consumption (father)			
No	22 (36.1)	8 (22.9)	0.179
Yes	39 (63.9)	27 (77.1)	+
Mobile use (father)			
No	6 (9.8)	0 (0.0)	0.085
Yes	55 (90.2)	34 (100.0)	*
Daily duration of mobile use (father)			
<40'	27 (49.1)	9 (27.3)	0.044
>40'	28 (50.9)	24 (72.7)	+
Use or contact with industrial solvents or other substances (father)			
No	47 (79.7)	23 (65.7)	0.134
Yes	12 (20.3)	12 (34.3)	+
Smoking (mother)			
No	27 (43.5)	19 (54.3)	0.309
Yes	35 (56.5)	16 (45.7)	+
Alcohol consumption (mother)			
No	37 (59.7)	21 (60.0)	0.975
Yes	25 (40.3)	14 (40.0)	+
Mobile use (mother)			
No	11 (17.7)	0 (0.0)	0.007
Yes	51 (82.3)	35 (100.0)	*
Daily duration of mobile use (mother)			
<20'	23 (45.1)	14 (40.0)	0.639
>20'	28 (54.9)	21 (60.0)	+
Use or contact with industrial solvents or other substances (mother)			
No	13 (21.0)	9 (25.7)	0.592
Yes	49 (79.0)	26 (74.3)	+
Maternal contact with ionizing radiation			
No	45 (72.6)	28 (80.0)	0.416
Yes	17 (27.4)	7 (20.0)	+
During pregnancy (mother)			
Smoking			
No	47 (75.8)	30 (85.7)	0.247
Yes	15 (24.2)	5 (14.3)	+
Alcohol consumption			
No	54 (87.1)	28 (80.0)	0.353
Yes	8 (12.9)	7 (20.0)	+
Mobile use			
No	12 (19.4)	0 (0.0)	0.004
Yes	50 (80.6)	35 (100.0)	*
Daily duration of mobile use			
<20'	29 (58.0)	17 (48.6)	0.391
>20'	21 (42.0)	18 (51.4)	+
Use or contact with industrial solvents or other substances			
No	29 (49.2)	17 (48.6)	0.957
Yes	30 (50.8)	18 (51.4)	+
Maternal contact with ionizing radiation			
No	60 (96.8)	34 (97.1)	1.000
Yes	2 (3.2)	1 (2.9)	*
Maternal exposure to drugs during pregnancy			
No	53 (85.5)	19 (54.3)	0.001
Yes	9 (14.5)	16 (45.7)	+

[+]Pearson's chi-square test; *Fisher's exact test

Table 5
Adjusted odds ratio for craniosynostosis vs control-group, derived from stepwise multiple logistic regression analysis.

	aOR (95% CI) *	p-value
Maternal use of medication during pregnancy	6.34 (2.12–19.03)	0.001
Maternal use of oral progesterone (Utrogestan®) during pregnancy	4.04 (1.2–13.59)	0.024

‡Adjusted odds Ratio (95% Confidence Interval)

far. In the present study, univariate analysis showed that mobile phone use from both parents independently was associated with and increased unadjusted risk for CS versus controls. In the current study, it was decided to be included the fathers' use of phone as a risk factor, as large part of this usage is in proximity to the mother and the fetus if during pregnancy. Fragopoulou et al. [12] showed that exposure of mouse embryos to mobile phone radiation could affect the cranial bones and thoracic cage ribs' ossification process. However, adjusted risk of mobile use was not at a significant level for either parent, and most human-based studies have yet to prove an association between mobile radiation and birth defects.

In the present study, the only significant high-risk factor in logistic regression analysis was the maternal use of medication and particularly, the use of progesterone during pregnancy. Medication and maternal progesterone use were associated with an adjusted 6-fold and 4-fold risk for CS compared to controls. A plethora of studies associated the use of specific medication with birth defects [13–17]. For instance, fetal exposure to valproate during pregnancy is associated with metopic suture CS and subsequent trigonocephaly [13], while maternal treatment with opioid analgesics has been associated with increased risk of various birth anomalies, such as septal defect, spina bifida etc. [14]. A substance that has been under close investigation for CS is a thyroid hormone, the thyroxine (T4). Excess levels of thyroid hormones contribute to an accelerated suture fusion, as witnessed in juvenile thyrotoxicosis [15, 16]. In Rasmussen et al. case control study, the maternal hyperthyroidism (Graves' disease) or the hypothyroidism's treatment with synthetic T4 supplementation was associated with CS [17]. A recent retrospective study [18] demonstrated that premature suture fusion is associated with gestational diabetes, therefore insulin use on one hand or poor blood glucose control on the other could also play an important role in CS occurrence.

The current study records the oral progesterone's use as a potential risk factor for CS. Progesterone is an important hormone in the reproduction process that prepares the endometrium for a potential pregnancy and prevents uterus' muscles contractions. It is often prescribed by obstetricians in early pregnancy to help prevent miscarriages and is considered safe. An infantile case with premature sutural fusion was first described by Reifenstein [19]. In that case, the mother's infant 17a-hydroxyprogesterone intake for abortion was considered unrelated to the CS [19]. In another case of multiple synostoses, including CS, the mother was treated with progesterone injections for atypical genital bleeding [20]. Andley-Bixler syndrome is an entity that encompasses CS and is associated with impaired steroid synthesis and FGFR mutations, whilst some cases possibly have P450 oxidoreductase deficiency and elevation of 17-OH-progesterone levels with normal basal cortisol levels [21]. However, the current detailed literature review did not reveal any research that would investigate progesterone intake as a potential CS risk factor.

4.1. Study limitations

The current study has several limitations. The questionnaire collected no data on the dosages of oral progesterone used at every case, therefore no subgroup analysis and correlation could be made regarding different medication's doses. Despite Agia Sophia Children's Hospital having received most cases from all around the country, the sample size is relatively small, owing to the relative rarity of CS cases in Greek children population and low birth rate. This is one of the reasons that the study's period investigation was extended to 5 years. By further expanding it, more cases could have been added, but there would have been a higher risk for recall bias in the parents' interviews. This mentioned, a higher recall bias exists in parents' interviews in the control group, since the mean age of subjects is statistically significantly higher in that group. Lastly, including 143 questions, the questionnaire was meant to incorporate all possible factors associated with the CS birth defect, but at this stretched length fatigue could cause a response burden and bias. To ensure this was not the case, face to face interviews with parents were conducted after appointments were made at a time of their convenience.

5. Conclusion

Non-syndromic CS is an entity with increasing prevalence, but without an established etiology. In the current study was shed on light that the maternal use of medication during pregnancy and progesterone is associated with an increased risk of infantile CS. Due to the relative low frequency of CS and the small sample of the study, further research is warranted with a larger sample from multiple centers.

Ethical statement

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner.

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Author contributions

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Declaration of Competing Interest

None.

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