Birth characteristics and childhood malignant central nervous sytem tumors: the ESCALE study (French Society for Childhood Cancer).

Nathalie Mallol-Mesnard, Florence Menegaux, Brigitte Lacour, Olivier Hartmann, Didier Frappaz, François Doz, Anne-Isabelle Bertozzi, Pascal Chastagner, Denis Hémon, Jacqueline Clavel

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Short title: Childhood CNS tumours and birth characteristics.

Category: original article

Condensed abstract: Pre- and perinatal characteristics (birth weight, gestational age, birth order, breastfeeding, congenital anomalies, use of assisted reproductive technology, and foetal losses) were obtained for 209 cases of childhood malignant central nervous system tumour and 1681 frequency matched controls. The results suggest an association with a maternal history of miscarriages.

Authors:

Nathalie Mallol-Mesnard (MD)[1,2], Florence Menegaux (MD, PhD)[1,2], Brigitte Lacour (MD)[1,2,3], Olivier Hartmann (MD)[4], Didier Frappaz (MD)[5], François Doz (MD)[6], Anne-Isabelle Bertozzi (MD)[7], Pascal Chastagner (MD)[8], Denis Hémon (PhD)[1,2], Jacqueline Clavel (MD, PhD)[1,2,9]

Affiliations:

[1]INSERM, U754, Villejuif, France. [2]Univ Paris-Sud, UMR-S754, IFR69, Villejuif, France. [3]Registre National des Tumeurs solides de l'Enfant, Nancy, France. [4]Institut Gustave Roussy, Villejuif, France. [5]Centre Léon Bérard, Lyon, France. [6]Institut Curie, Paris, France. [7]Hôpital des Enfants, Toulouse, France. [8]Hôpital d'Enfants, Vandoeuvre les Nancy, France. [9]Registre National des Hémopathies malignes de l'Enfant, Villejuif, France.

*SFCE: Société Française de lutte contre les Cancers de l'Enfant et de l'Adolescent

Corresponding author:

Jacqueline Clavel

Inserm U754

16, av. Paul Vaillant-Couturier

F-94807 VILLEJUIF Cedex

Tel: 33 1 45 59 50 38; Fax: 33 1 45 59 60 20; E-mail: clavel@vjf.inserm.fr

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Liste of abbreviations

ESCALE: Etude Sur les CAncers et les Leucémies de l'Enfant (Study on childhood cancers and leukemia)

EUROCAT: European Surveillance of Congenital Anomalies

ICCC: International Classification on Childhhod Cancer

ICD-I-3: International Classification of Diseases for Oncolgy, Third Edition

RNHE: Registre National des Hémopathies malignes de l'Enfant (National Registry of Childhood Haematological Cancers)

RNTSE: Registre National des Tumeurs Solides de l'Enfant (National Registry of Childhood Solid Tumours)

SFCE: Société Française de lutte contre les Cancers de l'Enfant et de l'adolescent (French society for childhood cancer)

Abstract

Background: Determining the role of pre- and perinatal factors in the aetiology of childhood malignant central nervous (CNS) tumours, using data from the French national case-control study, ESCALE. **Methods**: ESCALE included all children in France less than 15 years old with a diagnosis of acute leukaemia, lymphoma, malignant CNS tumour, or neuroblastoma (2003-2004). In all, 209 malignant CNS tumour cases (80% of the eligible cases) and 1681 population-based controls (71%) were included using quotas ensuring frequency matching with the cases by age and gender. Case and control mothers were interviewed using a standardised telephone interview, which elicited birth characteristics, congenital malformation, maternal reproductive history, and use of assisted reproductive technologies for the index child. **Results**: The cases and controls did not differ in terms of gestational age at birth, birth weight, birth order, breastfeeding, or parental age at birth. There was no association between assisted reproduction for the index child and malignant CNS tumour (OR = 1.1 [0.6-2.2]). A positive association between a maternal history of one miscarriage and malignant CNS tumour was observed (OR = 1.4 [1.0-2.0], $p<0.05$), especially for glial cell tumours (other glioma: OR = 2.0 [1.1-3.6]). **Conclusion**: The results suggest a possible association between a maternal history of one miscarriage and the risk of malignant CNS tumour.

Keywords: Epidemiology ; risk factors ; childhood CNS tumour ; birth characteristics

Introduction

Central Nervous System [CNS] tumours are the most common childhood cancer, after leukaemia, in developed countries [1], accounting for 20 to 25% of all childhood neoplasms. In France, about 200 new cases of malignant CNS tumours are diagnosed each year [2]. Most of the cases emerge before the age of 5 years, suggesting that antenatal, perinatal, or early postnatal exposures may be considered potential risk factors [3]. Most of the central nervous system's development occurs during foetal life and over the first 2 or 3 years of extrauterine life, with a trend toward heterogeneity of the various types of central nervous system cells. It is therefore important to consider the period of exposure as well as the type of exposure suspected. Apart from ionizing radiation and a few rare genetic syndromes, the aetiology of childhood CNS tumours is largely unknown. Maternal reproductive history, such as foetal losses and assisted reproduction technologies for the index child, has often been studied, but associations with CNS tumors have rarely been observed. Birth characteristics, such as gestational age, birth weight, parent's age at birth, birth order and congenital malformations, have also been studied. Only congenital malformations seem to be frequently associated with CNS tumors [4, 5]. This paper reports the results for maternal reproductive history, birth characteristics, and the risk of childhood malignant CNS tumors, based on data from the ESCALE study.

Materials and methods

ESCALE is a French national population-based case-control study conducted in 2003 and 2004, which addressed 4 childhood neoplastic diseases (leukaemia, lymphoma, neuroblastoma, and malignant central nervous system tumour) and infectious, environmental, and genetic risk factors. This paper concerns the cases of malignant central nervous system tumours.

Study population and data collection

The design of the study has already been published elsewhere [6]. The cases were all children (0-14 years) whose malignant central nervous system tumour was diagnosed between 2003 and 2004. The cases were living in France at the time of diagnosis. All the cases were recruited directly by investigators assigned to each French paediatric oncology hospital

department with the support of the two National Registries of childhood cancer: the National Registry of Childhood Haematological Cancers (RNHE) [7] and the National Registry of Childhood Solid Tumours (RNTSE) [8]. The diagnoses were confirmed by crosschecking with the RNTSE, which was also able to give a histological confirmation for 81% of the cases and a clinical/radiological confirmation for 16%. All the cases have been classified into 4 groups using the third version of the International Classification of Childhood Cancer (ICCC) based on the ICD-O-3 [9]: embryonal tumours (ICD-O-3 codes 9470/3, 9471/3, 9473/3, 9474/3, 9480/3, 9508/3), astrocytomas (codes 9380/3, 9400/3, 9401/3, 941/3, 9420/3, 9424/3, 9440/3), other gliomas (codes 9380/3, 9381/3, 9382/3, 9430/3, 9450/3, 9451/3), and ependymomas (codes 9390/3-9393/3).

For ethical reasons, children who had died or who were receiving palliative care before the inclusion date were not eligible. The cases that were adopted, whose mothers were not French-speaking or who had serious psychiatric disorder were not eligible. Out of the 343 cases of malignant central nervous system tumours (with a /3 behaviour ICD-O-3 codes) diagnosed in France from January 1, 2003, to December 31, 2004, 82 were therefore not eligible (57 early deaths, 1 child receiving palliative care, 14 non-French speaking mothers, 5 non-biological mothers, and 5 psychiatric disorders). Out of the 261 eligible cases, 19 refused to participate and 33 could not be contacted by interviewers despite repeated attempts. Finally, 209 (80%) of the eligible cases of malignant CNS tumour were included in the study.

The control group was selected from the French population by sampling from 60,000 representative addresses taken from the French national telephone directory plus unlisted phone numbers generated randomly. Age and gender quotas were applied to ensure the same age and sex distribution as the group of cases. Additional quotas for the number of children living in the household, based on the last population census, were used to improve the comparability of the controls with the French population with regard to birth order. The latter is related to a number of variables of interest, such as early day-care or breast-feeding, and might otherwise have been biased by sampling. Out of the 50,217 phone numbers contacted, 46,994 were ineligible numbers (22,584 business or inactive numbers, 18,456 households without children, 5,277 outside of the quotas, and 677 with no living, French-speaking biological mother). The eligibility of 862 phone numbers whose owners hung up too early could not be determined. Out of the 2361 remaining

eligible controls, 679 parents refused and 1 child had a prior history of neuroblastoma. Finally, 1681 controls (71%) were included in the study.

The case and control mothers' interviews were conducted by telephone by trained interviewers using the same standardised questionnaire. The interview elicited data on demographic and socio-economic characteristics, parental occupational history, childhood environment, familial and personal medical history, and history of pregnancy. The mother's obstetric history was specifically described: foetal losses (spontaneous, voluntary, or therapeutic) and assisted reproduction for the index child. The mothers were also asked to describe the characteristics of the index child at birth: gestational age, birth weight, parents' age at birth, birth order, breastfeeding, and presence and site of congenital malformations. Malformations were classified as major or minor malformations using the European Surveillance of Congenital Anomalies (EUROCAT) classification [10].

Statistical analysis

The SAS® software package (version 9, Cary, North Carolina) was used for all the analyses. Analyses were carried out for all central nervous system tumours considered malignant, in combination and separately for each large group of malignant CNS tumours: ependymomas, embryonal tumours, astrocytomas, and other gliomas. All the variables were treated as categorical variables. Odds ratios (OR) and their 95% confidence intervals (95% CI) were estimated using unconditional logistic regression, closely adjusted for age and gender. Polytomous logistic regression adjusted for age and gender was also used to study the large groups of CNS tumours simultaneously. Additional adjustments for potential confounding factors and mutual adjustments were also made.

Results

For the 209 cases, the diagnoses were as follows: ependymoma in 33 cases; embryonal tumours in 100 cases; high grade astrocytoma in 26 cases; other glioma in 45 cases; and other types of CNS tumour in 5 cases. In 7 cases, type 1 neurofibromatosis (NF1) had been diagnosed.

The cases did not differ from the controls with respect to gender (table I). Since age quotas for selection of the controls had been defined to enable comparison with the whole case

group, there was a small age discrepancy between the CNS cases and controls, particularly for very young children. There were, however, at least 5 controls for each case in each age group, and the mean ages of the cases and controls were very similar (6.3 vs. 6.0, p = 0.4). The cases and controls were also similar with respect to the parents' marital status, educational level and socioeconomic category (table I). The number of children living in the household, made comparable to that in the French population by quotas, differed significantly between cases and controls: single children were more frequent for the controls than for the cases.

The cases' mothers reported slightly more frequent history of one miscarriage (OR = 1.4 [1.0-2.0], $p<0.05$), but this association was restricted to some glial cell tumours (other gliomas: OR = 2.0 [1.1-3.6]) (table II). When mothers who had also had voluntary or therapeutic abortions were excluded, the results were unchanged. Childhood CNS tumour was not related to voluntary or therapeutic abortion, except for the ependymomas, which were associated with voluntary abortion. There was no association between childhood CNS tumour and assisted reproduction, irrespective of the type of tumour.

Overall, gestational age was not associated with CNS tumour, except for embryonal tumours, which were significantly associated with a gestational age at birth of less than 37 weeks (table III). No association between malignant CNS tumours and birth weight or parental age at birth or breast-feeding was observed, irrespective of the type of tumour. An isolated association between birth order and embryonal tumours was observed, with a higher OR for second born children but not for children born subsequently.

A total of 8 cases presented with congenital malformations, 6 of which were major malformations (1 cleft lip, 1 cleft palate, 1 congenital malformation of the circulatory system, 1 congenital dislocation of the hip, 1 child with webbed toes, and 1 child with spade-like hands) and 2 of which were minor (1 non-neoplastic giant congenital nevus and 1 case of depressions in the skull). No association between major or minor malformations and CNS tumour was evidenced (table III). However, malformations, and especially major malformations, were more often positively, but non-significantly, associated with glial cell tumours (astrocytomas: OR = 1.9 [0.2-14], other gliomas: OR = 2.9 [0.9-10]) than with the other types of CNS tumour.

The results were unchanged after adjusting for the parents' educational level and socioeconomic category. The results were also unchanged when maternal reproductive history

and birth characteristics were included in the same model. Lastly, the exclusion of cases with type 1 neurofibromatosis did not modify the results.

Discussion

In short, the present study did not provide evidence of any association between malignant CNS tumours and gestational age at birth, birth weight, birth order, breast-feeding, parental age at birth, or medically assisted reproduction. Glial cell tumours (astrocytoma or other glioma) were significantly associated with a maternal history of miscarriages, and, to a lesser extent and not significantly, with the existence of major congenital malformations.

With a statistical power of 80% and an α error of 5%, the study was able to detect odds ratios from 1.5 (30% exposed controls) to 2.2 (5% exposed controls). The statistical power, however, was lower for subtype differences, particularly for uncommon exposures such as malformations.

All cases were identified directly by the network of investigators working with the 2 French National Registries of Childhood Cancer (RNHE and RNTSE), making selection bias due to the case identification process unlikely. The ineligibility of cases who had died or were under palliative care may have induced a survival bias. To the authors' knowledge, however, none of the variables of interest are known to be survival factors, after accounting for age and tumour type [11]. The study included 19 children who died early, after the interview. They were younger at diagnosis than the children who survived (5.4 vs. 6.1 years old), but comparable, although the numbers were small, with regard to the other characteristics. Therefore, the exclusion of early deaths is unlikely to have induced a major selection bias. The 52 cases (20%) who did not answer the questionnaire had similar age and gender distributions to those of the respondent cases.

All the diagnoses were ascertained by the National Childhood Registry of Solid Tumours (RNTSE) and confirmed by histology (81%) and radiology (16%). The results did not change after exclusion of cases whose tumour had not been histologically confirmed.

The controls were selected from the general population using the national telephone directory as a random basis together with randomly generated unlisted numbers. The sampling process also made the controls similar to the French population in terms of number of children

living in the household and, subsequently, in terms of birth order, when compared with the national perinatal surveys [12, 13]. Comparison with those surveys also showed that the controls were very similar to the French population in terms of paternal age at birth, mother's educational level, voluntary abortion, assisted reproduction, gestational age at birth and birth weight, and maternal reproductive history. The controls' mothers were slightly older than in the overall population. However, no association between the mother's age at birth and childhood CNS tumour was observed and adjusting for that variable did not modify the results. The proportion of congenital malformations in the controls (3.4%) was very close to what was expected on the basis of the Paris Registry of Congenital Malformations (2.2% to 3.2% for children born between 1988 and 2000) [14].

In order to avoid misclassification with respect to gestational age, birth weight, abortions, and assisted reproduction, only biological mothers were interviewed and identical questionnaires were used for the cases and controls. The frequent examinations and computed tomography and ultrasound scans of children with brain tumours are liable to promote malformation detection and reporting, and may have led to differential misclassification. However, this probably mainly concerns minor, rather than major, malformations and very young children. Major malformations are unlikely to remain undetected after the age of one year. In this study, all the cases with malformations were at least one year old. Because the information on malformations was only given by the mothers, ascertainment may have been incomplete, but similarly, for both the cases and controls.

As was the case in this study, the previous studies did not evidence any association between birth order and childhood CNS tumour [15-25]. The association between embryonal tumours and second born children observed in the present study was isolated, with no linear trend with increasing birth order, and would appear to have no particular biological plausibility.

A potential link between birth weight and childhood leukemia has been suggested in a meta-analysis of 18 studies [26] and in several studies which were not included in the meta-analysis [27-31]. Insulin-like growth factor has been proposed as a possible explanation [32]. For CNS tumours, no relationship with high birth weight was reported in most of the previous studies [17, 18, 21, 22, 33-37]. The only relationship with high birth weight was reported for astrocytomas [15, 19, 25]. When the results were reported separately for astrocytomas, they were discordant [15, 25].

Only 2 of the 10 previous studies [19, 20, 23, 25, 38-42] showed a positive relationship between CNS tumours and premature birth [40, 42]. As in the present study, one of those studies reported a relationship with medulloblastoma [42].

Several studies have suggested that breastfeeding may have a protective affect in childhood cancer [43], especially in childhood leukaemia. Nevertheless, none of the studies investigating the role of breastfeeding in childhood CNS tumours, including the present study, observed such inverse association [21, 23, 37, 40].

Most studies considering maternal history of foetal losses have not shown any association with CNS tumours [15, 16, 19-21, 23-25]. However, one study investigating malignant CNS tumours also reported a positive association with malignant astrocytoma [15]. A variety of terms were used in the previous studies and it is not always possible to distinguish between spontaneous, voluntary and therapeutic abortions. The terms used by the mothers themselves are probably not always reliable. In the present study, no association was found when all the types of foetal losses (spontaneous, therapeutic, and voluntary abortions) were considered together. The observed association between voluntary abortion and ependymoma remained stable after adjusting for well known confounding factors such as socioeconomic characteristics or smoking during pregnancy. It is therefore difficult to explain except by misclassification of the type of abortion.

Many studies have evidenced an association between congenital malformations and CNS tumours [4, 5, 44-46], sometimes with a stronger association when the malformation had a CNS site [44, 46]. In the present study, none of the controls and only one case presented with a brain malformation, and that malformation was minor. Congenital malformations have decreased in France since 1995, thanks to active prevention (folate supplementation) and early screening for major CNS malformations such as spina bifida, enabling therapeutic abortion [14].

To the authors' knowledge, only 3 studies on CNS tumour and medically assisted reproduction have been published. None of them reported any association [23, 47, 48]. More generally, no association between childhood malignancies and medically-assisted reproduction has ever been reported [49-52]. The present results are therefore consistent with those of the published studies.

Conclusion

The present study does not support a role of prematurity, birth weight, breastfeeding or parental age in the occurrence of malignant CNS tumours. It suggests that a maternal history of miscarriages may be associated with the risk of malignant CNS tumours.

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Table I: Characteristics of the cases and controls

	Cases n=209 (%)		Controls n=1681 (%)		Co/Ca[(a)] ratio	p
Histological subtypes						
Embryonal tumours	100	*(48)*				
Ependymomas	33	*(16)*				
Astrocytomas	26	*(12)*				
Other gliomas	45	*(21)*				
Other specified tumors	5	*(3)*				
Gender						ns[(b)]
Male	125	*(60)*	932	*(55)*		
Age at the reference date (years)						0.03[(b)]
< 2	34	*(16)*	369	*(22)*	10.5	
2	15	*(7)*	153	*(9)*	10.2	
3	17	*(8)*	166	*(10)*	9.8	
4	25	*(12)*	145	*(9)*	5.6	
5-6	34	*(16)*	228	*(14)*	6.5	
7-8	33	*(16)*	163	*(10)*	4.8	
9-11	27	*(13)*	225	*(13)*	8.3	
12-14	24	*(11)*	232	*(14)*	9.7	
Parent's marital status at interview						ns[(c)]
Married	191	*(92)*	1541	*(92)*		
Separated, divorced, widowed	4	*(2)*	65	*(4)*		
Single	14	*(7)*	75	*(5)*		
Paternal educational level						ns[(c)]
≤ High school	126	*(60)*	1063	*(63)*		
> High school	79	*(38)*	601	*(36)*		
missing data	4	*(2)*	17	*(1)*		
Maternal educational level						ns[(c)]
≤ High school	125	*(60)*	979	*(58)*		
> High school	84	*(40)*	701	*(42)*		
Socioprofessional categories						ns[(c)]
Intellectual and scientific jobs, intermediate profession	92	*(44)*	713	*(42)*		
Administrative employees and sales workers	51	*(24)*	477	*(28)*		
Service workers	29	*(13)*	215	*(13)*		
Farmers, agricultural, craftsmen and factory workers	37	*(18)*	274	*(16)*		

[(a)] Co/Ca ratio: Controls/Cases ratio
[(b)] Chi square test, ns: p>0.05
[(c)] Non-conditional logistic regression adjusted for age and gender

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Table II: Mother's obstetrical history and childhood central nervous tumours

	Controls n=1681 (%)		All CNS tumours n=209 (%)				Ependymomas (n=33)			Embryonal tumours (n=100)			Astrocytomas (n=26)			Other gliomas (n=45)		
	n	*(%)*	n	*(%)*	OR	[IC$_{95\%}$][(1)]	n	OR	[IC$_{95\%}$][(2)]	n	OR	[IC$_{95\%}$][(2)]	n	OR	[IC$_{95\%}$][(2)]	n	OR	[IC$_{95\%}$][(2)]
All foetal losses																		
No	1031	*(61)*	115	*(55)*	1.0	ref	20	1.0	ref	57	1.0	ref	12	1.0	ref	23	1.0	ref
Yes	650	*(39)*	94	*(45)*	1.3	[1.0-1.7]	13	1.1	[0.5-2.2]	43	1.2	[0.8-1.8]	14	1.8	[0.8-4.0]	22	1.5	[0.8-2.6]
1	403	*(24)*	58	*(28)*	1.3	[0.9-1.8]	8	1.1	[0.5-2.5]	26	1.2	[0.7-1.9]	10	2.2	[0.9-5.0]	12	1.3	[0.6-2.7]
2	247	*(15)*	36	*(17)*	1.3	[0.9-1.9]	5	1.1	[0.4-3.0]	17	1.2	[0.7-2.1]	4	1.3	[0.4-4.2]	10	1.7	[0.8-3.6]
Miscarriages																		
No	1239	*(74)*	142	*(68)*	1.0	ref	29	1.0	ref	68	1.0	ref	16	1.0	ref	26	1.0	ref
Yes	442	*(26)*	67	*(32)*	1.3	[1.0-1.8]	4	0.4	[0.1-1.1]	32	1.3	[0.9-2.0]	10	1.7	[0.8-3.8]	19	2.0	[1.1-3.6]
1	303	*(18)*	50	*(24)*	1.4*	[1.0-2.0]	2	0.3	[0.1-1.2]	24	1.4	[0.9-2.3]	10	2.5	[1.1-5.6]	12	1.8	[0.9-3.6]
≥ 2	138	*(8)*	17	*(8)*	1.1	[0.6-1.8]	2	0.6	[0.1-2.6]	8	1.1	[0.5-2.3]	0	-	-	7	2.4	[1.0-5.5]
Voluntary abortion																		
No	1429	*(85)*	173	*(83)*	1.0	ref	23	1.0	ref	85	1.0	ref	21	1.0	ref	39	1.0	ref
Yes	252	*(15)*	36	*(17)*	1.2	[0.8-1.7]	10	2.6	[1.2-5.7]	15	1.0	[0.5-1.7]	5	1.4	[0.5-3.8]	6	0.8	[0.4-2.0]
1	209	*(12)*	27	*(13)*	1.1	[0.7-1.6]	6	1.9	[0.7-4.6]	12	0.9	[0.5-1.8]	4	1.4	[0.5-4.1]	5	0.9	[0.3-2.2]
≥ 2	43	*(3)*	9	*(4)*	1.7	[0.8-3.6]	4	7.2	[2.3- 22]	3	1.1	[0.3-3.7]	1	1.5	[0.2- 12]	1	0.8	[0.1-5.9]
Therapeutic abortion																		
No	1594	*(95)*	203	*(97)*	1.0	ref	33	1.0	ref	97	1.0	ref	24	1.0	ref	44	1.0	ref
Yes	87	*(5)*	6	*(3)*	0.5	[0.2-1.2]	0	-	-	3	0.5	[0.2-1.8]	2	1.4	[0.3-6.2]	1	0.4	[0.1-2.8]
Assisted reproduction for the index child																		
No	1599	*(95)*	198	*(95)*	1.0	ref	29	1.0	ref	97	1.0	ref	25	1.0	ref	43	1.0	ref
Yes	82	*(5)*	11	*(5)*	1.1	[0.6-2.2]	4	2.6	[0.9-7.8]	3	0.6	[0.2-2.1]	1	0.8	[0.1-6.3]	2	0.9	[0.2-3.9]

[(1)] Non-conditional logistic regression adjusted on age and gender, [(2)] Non-conditional polytomic regression adjusted on age and gender

* $p<0.05$

435 **Table III:** Characteristics of children at birth and risk of childhood malignant central nervous tumours

	Controls n=1681 (%)		**All CNS tumours n=209 (%)**				**Ependymomas (n=33)**			**Embryonal tumours (n=100)**			**Astrocytomas (n=26)**			**Other gliomas (n=45)**		
	n	*(%)*	n	*(%)*	**OR**	$[IC_{95\%}]^{(1)}$	n	**OR**	$[IC_{95\%}]^{(2)}$	n	**OR**	$[IC_{95\%}]^{(2)}$	n	**OR**	$[IC_{95\%}]^{(2)}$	n	**OR**	$[IC_{95\%}]^{(2)}$
Gestational age																		
< 37 weeks	107	*(6)*	20	*(10)*	**1.6**	[0.8-2.9]	3	**1.5**	[0.4-6.2]	13	**2.5**	[1.1-5.4]	1	**0.4**	[0.1-3.6]	2	**0.6**	[0.1-3.1]
37-41 weeks	1515	*(91)*	177	*(87)*	**1.0**	**ref**	29	**1.0**	**ref**	83	**1.0**	**ref**	22	**1.0**	**ref**	39	**1.0**	**ref**
> 41 weeks	40	*(2)*	6	*(3)*	**1.4**	[0.6-3.3]	1	**1.4**	[0.2- 11]	1	**0.5**	[0.1-3.8]	1	**1.9**	[0.2- 15]	3	**2.7**	[0.8-9.3]
Birth weight																		
< 2500	94	*(6)*	16	*(7)*	**1.0**	[0.5-2.5]	2	**0.8**	[0.1-4.3]	8	**0.9**	[0.3-2.3]	3	**2.2**	[0.4- 11]	3	**1.7**	[0.4-7.1]
2500-4000	1451	*(86)*	178	*(85)*	**1.0**	**ref**	29	**1.0**	**ref**	83	**1.0**	**ref**	23	**1.0**	**ref**	38	**1.0**	**ref**
> 4000	135	*(8)*	15	*(7)*	**1.0**	[0.5-1.7]	2	**0.8**	[0.2-3.3]	9	**1.3**	[0.6-2.6]	0	**-**	-	4	**1.2**	[0.4-3.5]
Paternal Age																		
< 25	69	*(4)*	8	*(4)*	**1.0**	[0.4-2.0]	0	**-**	-	5	**1.3**	[0.5-3.3]	2	**1.9**	[0.4-8.4]	1	**0.5**	[0.1-3.9]
25-34	1109	*(66)*	135	*(64)*	**1.0**	**ref**	22	**1.0**	**ref**	63	**1.0**	**ref**	17	**1.0**	**ref**	30	**1.0**	**ref**
≥ 35	503	*(30)*	65	*(32)*	**1.1**	[0.8-1.5]	11	**1.0**	[0.5-2.1]	32	**1.2**	[0.7-1.8]	7	**1.0**	[0.4-2.4]	14	**1.1**	[0.6-2.1]
Maternal Age																		
< 25	163	*(10)*	17	*(8)*	**0.8**	[0.5-1.4]	2	**0.7**	[0.2-2.9]	7	**0.7**	[0.3-1.6]	3	**1.2**	[0.3-4.1]	5	**1.1**	[0.4-2.9]
25-34	1235	*(73)*	158	*(76)*	**1.0**	**ref**	25	**1.0**	**ref**	76	**1.0**	**ref**	19	**1.0**	**ref**	34	**1.0**	**ref**
≥ 35	283	*(17)*	34	*(16)*	**1.0**	[0.6-1.4]	6	**1.0**	[0.4-2.4]	17	**1.0**	[0.6-1.8]	4	**1.0**	[0.3-2.9]	6	**0.8**	[0.3-2.0]
Birth order																		
1	708	*(42)*	80	*(39)*	**1.0**	**ref**	13	**1.0**	**ref**	31	**1.0**	**ref**	11	**1.0**	**ref**	22	**1.0**	**ref**
2	608	*(36)*	94	*(44)*	**1.3**	[0.9-1.8]	15	**1.3**	[0.6-2.8]	52	**1.9**	[1.2-2.9]	13	**1.3**	[0.6-3.0]	14	**0.7**	[0.4-1.4]

3 +	365	*(22)*	35	*(17)*	**0.8**	[0.5-1.2]	5	**0.7**	[0.3-2.0]	17	**1.0**	[0.6-1.9]	2	**0.4**	[0.1-1.6]	9	**0.8**	[0.3-1.7]
Breast feeding(3)																		
Never	775	*(49)*	93	*(45)*	**1.0**	**ref**	16	**1.0**	**ref**	43	**1.0**	**ref**	12	**1.0**	**ref**	19	**1.0**	**ref**
Ever	816	*(51)*	112	*(55)*	**1.2**	[0.9-1.6]	16	**0.8**	[0.4-1.7]	55	**1.3**	[0.8-1.9]	13	**1.1**	[0.5-2.5]	26	**1.4**	[0.8-2.6]
Breast & Bottle	92	*(6)*	10	*(5)*	**0.9**	[0.5-1.9]	1	**0.5**	[0.1-3.6]	6	**1.3**	[0.5-3.1]	2	**1.5**	[0.3-7.0]	1	**0.5**	[0.1-3.5]
Breast only	724	*(45)*	102	*(50)*	**1.2**	[0.9-1.6]	15	**0.9**	[0.4-1.8]	49	**1.3**	[0.8-2.0]	11	**1.1**	[0.5-2.5]	25	**1.5**	[0.8-2.8]
Duration																		
≤ 3 months	484	*(30)*	67	*(33)*	**1.2**	[0.5-1.9]	9	**0.8**	[0.4-1.9]	28	**1.1**	[0.7-1.8]	10	**1.4**	[0.6-3.4]	19	**1.7**	[0.9-3.2]
> 3 months	240	*(15)*	35	*(17)*	**1.3**	[0.8-1.7]	6	**1.0**	[0.4-2.6]	21	**1.7**	[1.0-2.9]	1	**0.3**	[0.1-2.4]	6	**1.2**	[0.5-3.0]
Congenital malformations																		
No	1624	*(97)*	201	*(96)*	**1.0**	**ref**	32	**1.0**	**ref**	97	**1.0**	**ref**	25	**1.0**	**ref**	42	**1.0**	**ref**
Yes	57	*(3)*	8	*(4)*	**1.1**	[0.5-2.3]	1	**1.0**	[0.1-7.2]	3	**0.8**	[0.2-2.6]	1	**1.2**	[0.2-9.2]	3	**2.0**	[0.6-6.6]
Major	38	*(2)*	6	*(3)*	**1.2**	[0.5-2.9]	0	**-**	-	2	**0.8**	[0.2-3.5]	1	**1.9**	[0.2- 14]	3	**2.9**	[0.9- 10]

(1) Non-conditional logistic regression adjusted on age and gender; (2) Non-conditional polytomic regression adjusted on age and gender; (3) Analysis were performed in children older than 6 months