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**Factors relating to pregnancy and birth and the risk of childhood brain tumors:
Results from an Australian case-control study**

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Abstract

Background: Childhood brain tumors (CBT) are the leading cause of cancer death in children, yet their causes are largely unknown. This study investigated the association between maternal and birth characteristics and risk of CBT.

Procedures: Cases families were recruited from all 10 Australian pediatric oncology centers between 2005 and 2010. Control families were recruited via random-digit dialing, frequency matched to cases on the basis of child's age, sex and State of residence. Maternal and birth characteristics of children were ascertained by questionnaires. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated using unconditional logistic regression, adjusting for relevant confounders.

Results: For this analysis, 319 case children and 1079 control children were available. No association was found between risk of CBT and birth weight, fetal growth, birth order, gestational age, or maternal body mass index. The ORs for inadequate and excessive maternal gestational weight gain (GWG) (Institute of Medicine 2009 guidelines) were 1.8 (95% CI 1.2-2.6) and 1.4 (95% CI 1.0-2.1) respectively; similar findings for GWG were seen across categories of child's age, fetal growth, maternal body mass index and height, maternal smoking, and parental education. Risk of low grade glioma appeared increased with preterm birth (OR 1.6 (95% CI 0.8-3.1) and admission to neonatal intensive care (NICU) for >2 days (OR 1.7, 95% CI 0.9-3.6).

Conclusion: We found little evidence of associations between risk of CBT and most birth characteristics. The associations we observed with GWG, prematurity and NICU admission require corroboration in other studies.

INTRODUCTION

Childhood brain tumors (CBT) are the leading cause of cancer death in children, yet little is known of their etiology. The only known causes - some genetic syndromes and ionizing radiation to the head – account for less than 5% of cases [1]. The early onset of many CBT cases suggests that genetic, prenatal or perinatal factors are likely to be involved.

High birth weight has been investigated in a number of studies, and a recent meta-analysis of eight studies reported elevated summary ORs for birth weights over 4,000g for astrocytoma and medulloblastoma, but not ependymoma [2]. The results of subsequent studies have been inconsistent; some were null [3] and others found positive associations [4, 5]. The association between CBT risk and accelerated fetal growth (as distinct from birth weight *per se*) has only been examined in three previous studies, all of which found little evidence of an association [5-7]. Other perinatal characteristics such as birth order and gestational age [3, 8-10] and assisted reproductive technology (ART) [3] have been investigated, but the evidence for associations with these factors is inconsistent or weak.

The aim of this study was to investigate associations between maternal and birth characteristics and risk of CBT in an Australian case-control study. In particular, we investigated appropriateness of maternal gestational weight gain (GWG) during pregnancy assessed using the 2009 Institute of Medicine guidelines [11], which has not been previously reported. We also sought to investigate these relationships by tumor subtype.

METHODS

The Australian Study of Causes of CBT in Children (AUS-CBT) was a national, population-based, multi-centre case-control study. It aimed to investigate genetic, dietary and environmental risk factors for CBT, and their interactions. Details of study methods have been published previously [12]. Briefly, children who had a biological parent available with adequate English skills were eligible to participate. Case families were identified through all ten pediatric oncology centers in Australia, where virtually all Australian children with CBT are treated. The study was approved by the ten hospital research ethics committees.

Data on birth weight, birth order, gestational age, maternal age, smoking habit, the presence of birth defects and plurality were collected in mailed exposure questionnaires. Additional information about type(s) of birth defect, the use of ART (in vitro fertilization, gamete intra-fallopian transfer, intracytoplasmic sperm injection and/or ovarian hormone stimulation) in the child's conception, and stays of more than two days in a neonatal intensive care unit (NICU) was subsequently obtained in a computer-assisted telephone interview (CATI). Data on

maternal height, pre-pregnancy weight, and GWG were collected in the mother's dietary questionnaire. Mothers who did not complete these surveys were asked to provide basic demographic information, child's birth weight and gestational age in a brief telephone interview.

Fetal growth, as distinct from birth weight *per se*, was characterized in two ways. The first was percentage of optimal birth weight (POBW) – the ratio of observed birth weight to 'optimal birth weight' (OBW) at the estimated gestational age at birth [13]. Briefly, OBW is estimated from a regression equation including terms for gestational age, maternal height, parity and infant sex that was derived from a population of singleton births without any recorded risk factors for intrauterine growth restriction. POBW is similar to the ratio of observed-to-expected weight for gestational age, with OBW substituted for expected weight. The average height for both case and control mothers (165cm) was assigned to the 12 case and 223 control mothers for whom this variable was missing.

The second measure of fetal growth was birth weight for gestational age. Children were defined as large-for-gestational age (LGA) or small-for-gestational age (SGA) if they were above the 90th or below the 10th percentile of birth weight (respectively) for gestational age, as defined by population-based sex-specific birth weight centiles [14]. Birth weight was also examined as a categorical variable. Birth order, gestational age, use of ART, and NICU admissions were examined as categorical variables.

Maternal body mass index (BMI) and gestational weight gain were available for mothers who had completed a dietary questionnaire in addition to the exposure questionnaire. Maternal pre-pregnancy BMI (from maternal weight 6 months prior to the index pregnancy) was categorised as <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), 30+ (obese).

Appropriateness of gestational weight gain (GWG) was categorised using criteria from the 2009 Institute of Medicine (IOM) guidelines on GWG, which aim to optimize health outcomes in the child and the mother [11]. These criteria vary by pre-pregnancy BMI: recommended (appropriate) GWG is 12.7-18.2 kg for underweight women, 11.4-15.9 kg for women with normal BMI, 6.8-11.4 kg for overweight women, and 5-9.1 kg for obese women. Weight gain below these levels is classified as inadequate GWG and weight gain above them as excessive GWG.

Statistical analysis

Unconditional logistic regression analysis in PASW Statistics 18 (IBM® SPSS® software, Armonk, New York) was used to investigate the association between birth characteristics and

CBT risk. Odds ratios (ORs) for birth weight, gestational age and birth order were estimated in a multivariate model. POBW was modeled linearly as a continuous variable (after preliminary modeling with fractional polynomials indicated this was the most appropriate model) with odds ratios calculated for every 1SD increase. Maternal BMI and GWG were modeled separately from other birth characteristics, as data were only available for mothers who completed dietary questionnaires. Models of GWG excluded preterm (<37 weeks gestation) and multiple births, as it is unclear what constitutes adequate GWG in such pregnancies. All models were adjusted for the study matching factors – child’s age at diagnosis or recruitment (controls), sex and State of residence – and variables that were associated with case/control status and, in controls, with one or more of the independent variables under study. The final covariates for all independent variables are listed in the footnote to Table 2. Effect modification by child’s age of diagnosis and maternal smoking was explored by fitting interaction terms in the models and examining stratified results. Subgroup analyses were also undertaken for the two largest CBT subtypes – low grade gliomas and embryonal tumors.

RESULTS

Subject recruitment and data collection in Aus-CBT have been described previously [12]. Briefly, 730 eligible CBT cases diagnosed between 2005 and 2010 were identified, of whom 568 (78%) were invited and 374 (66% of invited, 51% of eligible) consented to take part. CBT subtypes were categorized by two pediatric oncologists as previously described [12]. During the study, 3624 eligible controls were identified through random-digit dialing, and 2255 of these agreed to participate. In accordance with age and sex frequency matching quotas, 1467 of these were recruited to the study. Of these, 335 case families and 1363 control families completed questionnaires; 319 cases and 1079 controls provided data on key exposures and confounders; 313 of these cases and 843 of these controls also provided data on height and weight for estimation of maternal BMI (Table I). Overall, the distributions of demographic characteristics were similar among cases and controls (Table I), although control mothers were more likely to be over 35 years of age and to have European ethnicity.

A comparison with population statistics [15] indicated that younger mothers may be under-represented in controls; therefore, maternal age was not analyzed as a risk factor, but was included as a covariate in our statistical models. There was little evidence of an association between risk of CBT and birth order, birth weight or POBW (Table II). For CBT overall, the OR for a 1 SD increase in POBW was 0.9 (95% CI 0.8-1.0), while the ORs for LGA and SGA were 0.8 (95% CI 0.5-1.2) and 0.8 (95% CI 0.5-1.2) respectively. The OR for POBW was similar when babies with high birth weight ($\geq 4000\text{g}$) were excluded from analysis (OR 0.9,

95% CI: 0.8-1.1 for a 1 SD increase). The OR for ART was below the null, but there were too few exposed cases to produce meaningful results (Table II). Maternal pre-pregnancy BMI was not associated with CBT risk. The results for these birth and maternal characteristics were similar across categories of the child's age at diagnosis or recruitment (Supplemental Table I) and maternal smoking status (Supplemental Table II).

There was evidence of positive associations between risk of low grade glioma and both gestational age <37 weeks (OR 1.6, 95% CI 0.8-3.1), and NICU admission >2 days (OR 1.7, 95% CI 0.9-3.6) (Table II). When these variables were considered together, the ORs for low grade glioma were highest in children who were both premature and had NICU admission >2days, although the CIs were wide (Table III) When low grade gliomas were excluded, the ORs for other types of CBT were close to unity. .

We examined the reasons given by the mothers for NICU admission; responses were coded as 'prematurity' (approximately 40% for both cases and controls), 'lung problems, pneumonia or breathing difficulties' (43% cases and 25% controls), and 'other'; multiple reasons were sometimes reported. After mutual adjustment, the ORs for low grade glioma associated with admission to NICU for the reasons above were, respectively, 2.7 (95% CI 0.8-9.5), 2.2 (95% CI 0.8-5.8) and 1.2 (95% CI 0.4-3.4). The corresponding findings for CBT overall were 1.4 (95% CI 0.5-3.6), 2.0 (95% CI 0.9-4.6) and 0.9 (95% CI 0.4-2.0) (results not tabulated).

The ORs for inadequate and excessive maternal GWG were 1.8 (95% CI 1.2-2.6) and 1.4 (95% CI 0.97-2.1) respectively (Table II). The ORs for GWG were similar across categories of child's age, maternal smoking, fetal growth, maternal BMI, maternal height, and parental education (Supplemental Table III). The distribution of our control mothers across GWG categories was similar to those reported in a recent Australian study [16].

DISCUSSION

Most of the associations we investigated were null. Inadequate and to a lesser extent excessive maternal GWG, however, appeared to be associated with an increased risk of CBT overall and of low grade glioma. There was also weak evidence of an increased risk of low grade glioma associated with preterm birth and NICU admission.

Our finding of an increased risk of low grade glioma associated with preterm birth was based on only 19 cases, and may be due to chance. Other studies have variously reported increased risks of specific CBT subtypes with preterm birth: embryonal tumors [3], ependymoma [17] and medulloblastoma [18], while Heuch and colleagues [9] reported a weak U-shaped association with gestational age for CBT overall. The reasons for the differences among

studies are not clear, but the small numbers in most CBT subtypes in individual studies are likely to lead to unstable and imprecise estimates. Our null findings for gestational age and risk of CBT overall were consistent with most previous studies [8, 10, 19-21].

The ORs associated with admission to a NICU for more than two days because of prematurity or respiratory problems were elevated, particularly for low grade glioma. While three previous studies [8, 21, 22] found no association between CBT risk and admission to a special care ward, two of these studies [8, 22] and another [20] reported at least weak evidence of positive associations with neonatal respiratory problems and/or related treatments. However, as in our study, the ORs in these studies were imprecise. Possible mechanisms for the observed associations include those involving the underlying condition itself, medications received or diagnostic procedures (eg. x-rays) administered for these conditions. Unfortunately, we do not have access to this information or to other data relating to the delivery, and are unable to explore these possibilities further.

The reasons for apparent association with GWG are not clear, and warrant further investigation. Unfortunately, data on medical complications of pregnancy or GWG composition were not collected in this study. Increased ORs for both inadequate and excessive GWG in the absence of increased ORs for SGA or LGA is biologically plausible. Maternal GWG had only a weak correlation with birth weight in controls ($r=0.09$). A normal term baby accounts only for approximately 30% of the total weight gained by the mother, with other factors, such as blood volume expansion, uterus and breast size increases, and fat-mass accretion making up a large percentage of the remainder [23]. The only previous study to examine GWG and risk of CBT found no association [8]. However, that study did not take account of pre-pregnancy BMI. This is important because women who are of low BMI at the start of their pregnancy are expected to gain more absolute weight than women who are of high BMI, and recording only absolute weight gain may not give an accurate indication of whether the GWG is appropriate [11]. It would also be beneficial for future studies to measure GWG composition and collect data on other aspects of maternal health during pregnancy. The lack of association we observed between birth weight and risk of CBT is consistent with some reports [3, 8, 20-22, 24], while other studies have reported increased risks with high birth weight for at least some CBT subtypes [4, 5, 9, 10, 17-19, 25, 26]. Our null finding for birth order is consistent with most previous studies [3, 9, 10, 18, 19, 21, 25], although McCredie et al [8] reported weak positive associations between being fourth (or later) born and risk of primitive neuroectodermal tumors, and two studies reported an increased risk of medulloblastoma [17] and high grade astrocytoma [20] in first born children.

A review of the risk of childhood cancers after assisted conception [27] concluded that there was little evidence of an increased risk, and cautioned that any positive associations seen may be related to underlying infertility. Few children in our study were conceived through ART, so we lacked power to detect any association between ART and risk of CBT, as did a previous similar study [3]. However, a recent cohort study of 26,692 Swedish children born after IVF observed 15 CNS tumors when 8.1 were expected (standardized incident rate: 1.8, 95% CI 1.0-3.1) [28]. Further investigation involving the use of data pooling could shed more light on this relationship.

This study has some limitations. Our participation fraction was lower among controls than cases, although cases and controls had similar distributions of socioeconomic and demographic factors. Data from government statistics [15] indicate that the distributions of birth weight, gestational age, prematurity, parity, and use of ART among our controls were similar to the general population. Therefore the results for these variables are unlikely to be due to selection bias, despite the lower participation among controls than cases. A higher proportion of data for maternal BMI and appropriateness of GWG was missing among controls than for the other variables. Among our control mothers, mothers with higher SES tended to have normal or low BMI and inadequate GWG, while excessive GWG was more common among overweight and obese mothers and mothers with lower SES. As previously reported, SES was higher in our participating controls than in the general population [12]. As a result, mothers with high BMI and excessive GWG were probably under-represented, and mothers with low BMI and inadequate GWG over-represented, in our control group. This may have led to inflated ORs for excessive GWG and underestimated ORs for inadequate GWG.

Birth weight and gestational age were reported by mothers and therefore subject to error, although these characteristics are generally reported accurately by mothers [29]. In addition, any misclassification is likely to be similar in cases and controls since these variables are not known to be related to childhood cancer. Information about NICU admissions, maternal BMI and gestational weight gain were reported by the mother and are therefore also prone to reporting error; again, however, this is unlikely to differ between cases and controls.

In conclusion, our findings suggest that admission to NICU for prematurity or respiratory problems, and inadequate (and possibly excessive) maternal GWG, may be associated with an increased risk of some types of CBT; however, these findings were based on small numbers and require corroboration in larger studies. Pooling of data relating to maternal and birth characteristics across studies would increase statistical power, particularly for the investigation of associations in specific CBT subtypes.

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Conflict of Interest Disclosure: The authors declare that they have no conflict of interest.

REFERENCES

1. Baldwin RT, and Preston-Martin S. Epidemiology of brain tumors in childhood--a review. *Toxicol Appl Pharmacol* 2004; 199: 118-131.
2. Harder T, Plagemann A, and Harder A. Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis. *Am J Epidemiol* 2008; 168: 366-373.
3. Mallol-Mesnard N, Menegaux F, Lacour B, et al. Birth characteristics and childhood malignant central nervous system tumors: the ESCALE study (French Society for Childhood Cancer). *Cancer Detect Prev* 2008; 32: 79-86.
4. Smith A, Lightfoot T, Simpson J, et al. Birth weight, sex and childhood cancer: A report from the United Kingdom Childhood Cancer Study. *Cancer Epidemiol* 2009; 33: 363-367.
5. Sprehe MR, Barahmani N, Cao Y, et al. Comparison of birth weight corrected for gestational age and birth weight alone in prediction of development of childhood leukemia and central nervous system tumors. *Pediatr Blood Cancer* 2010; 54: 242-249.
6. Schuz J, and Forman MR. Birthweight by gestational age and childhood cancer. *Cancer Causes Control* 2007; 18: 655-663.
7. Milne E, Laurvick CL, Blair E, et al. Fetal growth and the risk of childhood CNS tumors and lymphomas in Western Australia. *Int J Cancer* 2008; 123: 436-443.
8. McCredie M, Little J, Cotton S, et al. SEARCH international case-control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. *Paediatr Perinat Epidemiol* 1999; 13: 325-341.
9. Heuch JM, Heuch I, Akslen LA, et al. Risk of primary childhood brain tumors related to birth characteristics: a Norwegian prospective study. *Int J Cancer* 1998; 77: 498-503.
10. Mogren I, Malmer B, Tavelin B, et al. Reproductive factors have low impact on the risk of different primary brain tumours in offspring. *Neuroepidemiology* 2003; 22: 249-254.
11. IOM (Institute of Medicine) and NRC (National Research Council). Weight gain during pregnancy: Reexamining the guidelines. Washington DC: The National Academic Press; 2009p.
12. Milne E, Greenop KR, Bower C, et al. Maternal use of Folic Acid and Other Supplements and Risk of Childhood Brain Tumors *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1933-1941.

13. Blair E, Liu X, de Klerk N, et al. Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: an analysis of a total population perinatal database. *BMC Pediatrics* 2005: 5.
14. Roberts CL, and Lancaster PA. Australian national birthweight percentiles by gestational age. *Med J Aust* 1999; 170: 114-118.
15. Li Z, McNally L, Hilder L, et al. Australia's Mothers and Babies 2009. Perinatal Statistics Series no. 25. Cat. no. PER 52. Sydney: Australian Institute of Health and Welfare: National Perinatal Epidemiology and Statistics Unit, 2011.
16. de Jersey SJ, Nicholson JM, Callaway LK, et al. A prospective study of pregnancy weight gain in Australian women. *Aust N Z J Obstet Gynaecol* 2012; 52: 545-551.
17. Emerson JC, Malone KE, Daling JR, et al. Childhood brain tumor risk in relation to birth characteristics. *J Clin Epidemiol* 1991; 44: 1159-1166.
18. Schuz J, Kaletsch U, Kaatsch P, et al. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol* 2001; 36: 274-282.
19. Kuijten RR, Bunin GR, Nass CC, et al. Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res* 1990; 50: 2608-2612.
20. Linet MS, Gridley G, Cnattingius S, et al. Maternal and perinatal risk factors for childhood brain tumors (Sweden). *Cancer Causes Control* 1996; 7: 437-448.
21. McKinney PA, Juszczak E, Findlay E, et al. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. *Br J Cancer* 1999; 80: 1844-1851.
22. Fear NT, Roman E, Ansell P, et al. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control* 2001; 12: 443-449.
23. Pitkin RM. Nutritional support in obstetrics and gynecology. *Clin Obstet Gynecol* 1976; 19: 489-513.
24. Bunin GR, Buckley JD, Boesel CP, et al. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomarkers Prev* 1994; 3: 197-204.
25. Von Behren J, and Reynolds P. Birth characteristics and brain cancers in young children. *Int J Epidemiol* 2003; 32: 248-256.
26. Gold E, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol* 1979; 109: 309-319.

27. Lightfoot T, Bunch K, Ansell P, et al. Ovulation induction, assisted conception and childhood cancer. *Eur J Cancer* 2005; 41: 715-724.
28. Kallen B, Finnstrom O, Lindam A, et al. Cancer Risk in Children and Young Adults Conceived by In Vitro Fertilization. *Pediatrics* 2010; 126: 270-276.
29. Olson JE, Shu XO, Ross JA, et al. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. *Am J Epidemiol* 1997; 145: 58-67.