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Optic nerve hypoplasia in North America: a re-appraisal of perinatal risk factors

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ABSTRACT.

Purpose: **The purpose of this study is to describe and clarify the birth and prenatal characteristics of a large cohort of children with optic nerve hypoplasia.**

Methods: **This is a descriptive report of 204 patients aged ≤ 36 months and enrolled in a prospective study at the Children's Hospital Los Angeles. Birth characteristics, including complications, were abstracted from study files and medical records. Systematic maternal interviews were conducted to obtain detailed prenatal histories. National birth data were used for comparison with birth findings.**

Results: **Birth characteristics were unremarkable for birthweight and gestation, but significant for increased frequency of caesarean delivery and fetal and neonatal complications. Young maternal age and primaparity were dominating maternal features. Preterm labour, gestational vaginal bleeding, low maternal weight gain and weight loss during pregnancy were prevalent.**

Conclusions: **These findings confirm young maternal age and primaparity as associated risk factors, challenge many other suggested factors such as alcohol and drug abuse, and introduce potentially significant prenatal characteristics such as maternal weight loss and early gestational vaginal bleeding as aetiological correlates.**

Key words: de Morsier syndrome – aetiology – optic nerve hypoplasia – perinatal – prenatal – septo-optic dysplasia

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Introduction

Optic nerve hypoplasia (ONH) is a leading cause of childhood vision impairment in the USA and Europe, affecting as many as 12% of visually impaired children (Goggin & O'Keefe 1991; Blohme et al. 2000; Rahi & Cable 2003; Hatton et al. 2007) and one in 10 000 children under 16 years of age (Patel et al. 2006). Historically considered a rare occurrence, ONH, a congenital malformation, has increased six-fold in prevalence over the past four decades (Jan et al. 1977; Patel et al. 2006). This apparent epidemic is further supported by a Scandinavian report that found the prevalence of ONH to have risen dramatically amidst declines in all other causes of visual impairment in a homogeneous population over a 20-year period (Blohme et al. 2000).

The aetiology of this developmental anomaly is not understood, although numerous perinatal and prenatal pathogenic factors have been associated with ONH. A variety of the purported factors originated from reports of isolated cases (Table 1); however, many were born out of large case series, including: male (Siatkowski et al. 1997; Garcia et al. 2006) or female (Jan et al. 1977; Tornqvist et al. 2002) gender predisposition; being born small for gestational age (Tornqvist et al. 2002); preterm (Tornqvist et al. 2002; McNay et al. 2007) or post-term (Jan et al. 1977) gestation; low birthweight

Table 1. Anecdotal perinatal associations of optic nerve hypoplasia.

	References
Intrauterine growth restriction	Hellström et al. 1999; Birkebaek et al. 2003
Threatened abortion	Roberts-Harry et al. 1990
Twin–twin transfusion syndrome	Burke et al. 1991
Heritability	Hackenbruch et al. 1975; McNay et al. 2007
Temperature instability	McMahon & Braddock 2001
History of birth defects in multiparous women	Tornqvist et al. 2002
Recreational drugs	Hotchkiss & Green 1979; Margalith et al. 1984; Siatkowski et al. 1997; Patel et al. 2006
Antidepressants	Hellström et al. 1999; Tornqvist et al. 2002; Birkebaek et al. 2003
Anticonvulsants	Hoyt & Billson 1978; McMahon & Braddock 2001
Anti-emetics	Roberts-Harry et al. 1990
Antifungal agents	Tornqvist et al. 2002
Infertility treatment	Tornqvist et al. 2002
Quinine	McKinna 1966; Amatyakul et al. 2007
Prenatal complications	Hotchkiss & Green 1979; Reidl et al. 2002
Polyhydramnios	Hotchkiss & Green 1979
Viral infection	Hittner et al. 1976; Burke et al. 1991
Anaemia	Roberts-Harry et al. 1990; Burke et al. 1991
Trauma	Margalith et al. 1984

(Tornqvist et al. 2002; McNay et al. 2007); caesarean delivery (Tornqvist et al. 2002); neonatal complications, including jaundice (Margalith et al. 1984; Hellström et al. 2000; Fahnehjelm et al. 2003), hypoglycaemia (Margalith et al. 1984; Hellström et al. 2000; Fahnehjelm et al. 2003) and breathing problems (Margalith et al. 1984; Tornqvist et al. 2002); young maternal age (Margalith et al. 1984; Tornqvist et al. 2002); primaparity (Margalith et al. 1984; Tornqvist et al. 2002); prenatal exposure to smoking (Tornqvist et al. 2002) and alcohol (Strömland 1987; Hellström et al. 1999; Ribeiro et al. 2007), and prenatal complications including gestational diabetes (Kim et al. 1989) and toxaemia (Jan et al. 1977; Margalith et al. 1984; Burke et al. 1991).

Nearly all birth, maternal and prenatal findings associated with ONH originate from a retrospective review of records or selective samples. Only one previous study with a case-control design has systematically and sequentially investigated prenatal correlates in a large cohort of patients with ONH (Tornqvist et al. 2002). However, that study was confined to a subset of severe bilateral cases in Sweden and data were obtained from interviews conducted in the first trimester of pregnancy by a variety of midwives. Those data have the advantage of being relatively unbiased by recall or pregnancy outcomes, but the disadvantage of not capturing associations later in pregnancy. This is valid if one assumes that ONH is caused only by events that occur early in the first trimester. However, optic nerve axon growth proceeds well into the second trimester and the refinement of connections by programmed apoptosis continues throughout gestation. Thus, the possibility of later teratogenic events cannot be excluded.

The purpose of this study was to systematically describe the prenatal and early postnatal characteristics of a large and nearly sequential group of children with bilateral or unilateral ONH in North America in order to allow comparisons with previous studies in different populations to facilitate the generation of hypotheses for the aetiology of this apparently epidemic disease.

The Ophthalmology Clinic at the Children's Hospital Los Angeles (CHLA) is a referral centre for patients with ONH from across the USA. In 1992, a prospective study was implemented to examine prenatal characteristics and clinical risk factors in young children with ONH. Details on the design of the prospective study and the clinical characteristics and outcomes of this cohort have been reported elsewhere (Ahmad et al. 2006; Garcia-Filion et al. 2008). Herein we describe the birth and prenatal findings.

Materials and Methods

The parents or guardians of patients aged ≤ 36 months and diagnosed with ONH by a single neuro-ophthalmologist between 1992 and 2007 were asked to enrol their children in the study. The diagnosis of ONH was made by ophthalmoscopic confirmation of a small optic disc. Of the 319 patients with ONH referred during the study period, 252 were eligible for enrolment; 81% (204) consented to participation.

The study was approved by the Committee on Clinical Investigations (IRB) at CHLA. All subjects signed an informed consent to participation in research.

Birth characteristics

Birth information recorded during baseline ophthalmic or endocrine examination was abstracted from study files to describe: the distribution of birthweight, gestation and birth order; frequency of multiple gestation; frequency of vaginal versus caesarean delivery; distribution of maternal age at birth, and prevalence of prior terminations (spontaneous or induced). Race or ethnicity was based on parental report.

Birthweight was categorized as very low birthweight (VLBW) (< 1500 g), low birthweight (LBW) (1501–2500 g), normal birthweight (NBW) (2501–4000 g), and high birthweight (HBW) (> 4000 g). The categories for gestational age were very preterm (< 32 weeks), preterm (32–36 weeks), term (37–42 weeks) and post-term (> 42 weeks). Subjects with birthweights below the 10th percentile for gestational age were classified as being small for gestational age (SGA). Maternal ages at birth were grouped into 5-year age categories of < 20, 20–24, 25–29, 30–34, 35–39 and ≥ 40 years.

Birth complications

Histories of complications at delivery and in the neonatal period were obtained retrospectively from study files and medical records. Delivery complications included fetal distress, malpresentation (breech), use of instruments, emergency delivery by caesarean section and other complications. Neonatal complications included

jaundice, hypoglycaemia, distress and temperature instability.

Prenatal history

Systematic maternal interviews were conducted to elicit detailed information on reproductive history, index pregnancy characteristics, prenatal complications, maternal weight, exposure to smoking, alcohol and recreational drugs, and family history of eye disease. Adoptive mothers were excluded from participation. A standard interviewing protocol was employed for this aspect of the study. In line with the systematic methods used to assess exposure to smoking, alcohol and recreational drugs, measures to protect anonymity were taken and all participants were assured of confidentiality.

Reproductive histories collected data on: age at menarche and first sexual intercourse; menstrual cycle patterns during the 6 months prior to conception; history of birth defects in multiparous women, and use of hormonal contraceptives during the year prior to conception.

Index pregnancy characteristics included: whether or not the pregnancy had been planned; use of fertility treatment; initiation of prenatal care, and start and duration of use of prenatal vitamins.

Prenatal complications included: vaginal bleeding; threat of miscarriage; anaemia, and vaginal and urinary tract infections. The trimester in which any complication occurred was noted. Information on gestational diabetes, pregnancy-related hypertension, premature labour and systemic infections was not systematically requested and, thus, the presence of these and other miscellaneous complications was ascertained from study files.

Maternal weight characteristics included: pre-pregnancy body mass index (BMI) in kg/m^2 (estimated from self-reported pre-pregnancy height and weight); weight gain (highest weight during pregnancy minus pre-pregnancy weight), and weight loss (trimester and total weight lost). Pre-pregnancy BMI was categorized as < 19.8 (low), 19.8–26 (normal), and > 26 (high) according to the Institute of Medicine (IOM) BMI categories. Weight gain was categorized by pre-pregnancy BMI as being below, within or above the IOM guidelines for weight gain during pregnancy (Institute of Medicine 1990).

Mothers were asked about smoking habits in the year prior to conception and for each month of pregnancy. Regular use of cigarettes prior to pregnancy was defined as smoking at least one cigarette per day. Measurement of exposure to smoking during pregnancy included the average number of cigarettes smoked per week in each month of gestation. Questions about monthly alcohol use (number of drinks per week) during pregnancy were also asked. A drink was defined as 12 ounces of beer, 4 ounces of wine or 1 ounce of liquor. The average number of drinks of each type of alcohol consumed per week in each month of pregnancy was requested. Habitual use of alcohol during pregnancy was defined as having more than one drink per week beyond the second month of gestation. The frequency of gestational exposure to any alcohol during the first trimester is reported.

Data were collected on the monthly use of over-the-counter (OTC) (Hotchkiss and Green 1979) and prescription medications and recreational drugs (marijuana, lysergic acid diethylamide [LSD], crack, cocaine and opiates) during pregnancy. The OTC and prescription medications assessed included analgesics (non-steroidal anti-inflammatory drugs, acetaminophen and narcotics), vitamins (other than prenatal), antibiotics, cough or cold medications, anti-histamines, anti-nausea medications, antacids and laxatives, diet medications, asthma medications, anti-epilepsy drugs, sedatives, psychotropics (e.g. for depression, anxiety, attention-deficit hyperactivity disorder), cortisone, insulin, thyroid hormone and Retin-A. The timeframe of drug exposure is presented for the first two trimesters.

Family history of eye disease including ONH, strabismus, amblyopia and other eye problems was sought.

Statistical analysis

Birth characteristics and complications were compared with population-based normative birth data reported by the US Centers for Disease Control National Center for Health Statistics. National birth statistics are based on a registry of data recorded during the perinatal period using a standard questionnaire. The study was conducted over a 14-year (1992–2007) period and 48% of subjects were born prior to 2000; therefore, the 2000 national birth report was used for comparison (Martin et al. 2002). Subjects for whom data on birth characteristics were unavailable were excluded from the relevant analyses.

Independence of categorical variables was tested by Fisher's exact test. Wilcoxon rank-sum test was used to compare the distribution of continuous variables between groups. Maternal age at birth is presented as the mean ± standard deviation; differences with normative data were determined with a one-sample *t*-test. Differences in binomial variables from reference statistics were compared using a one-sample probability test with exact estimates of significance. Statistical significance was established at $p < 0.05$.

Results

Characteristics of the study cohort are presented in Table 2. The gender distribution was similar to national data ($p = 0.89$, binomial probability test). Compared with the clinic's patient population, the study sample included significantly more White subjects (30% versus 3%; $p < 0.001$), fewer Hispanics (46% versus 62%; $p < 0.001$), fewer Asia-Pacific Islanders (2% versus 6%; $p = 0.001$), fewer subjects classified as being of other or mixed race (13% versus 22%; $p = 0.001$), and equal numbers of African-Americans (6% versus 5%; $p = 0.24$) and subjects of unknown race or ethnicity (3% versus 2%; $p = 0.13$).

Birth findings

Characteristics

Table 3 summarizes abstracted data on infant and maternal characteristics at birth.

Six cases (3%) (all with bilateral ONH) resulted from multiple gestations (all dizygotic) and included five twins and one triplet. Three of these subjects had healthy siblings; of the remaining three, one had a sibling with fatal congenital heart malformations, one suffered a vanishing twin at

Table 2. Characteristics of the study cohort (n = 204).

	n	%
Male	103	51
Adopted	12	6
Race/ethnicity		
White	61	30
Hispanic	94	46
African-American	13	6
Asian-Pacific Islander	3	2
Other	26	13
Unknown	7	3
Referral source		
Endocrinologist	14	7
Neurologist	8	4
Ophthalmologist	56	28
Optometrist	3	2
Paediatrician	25	12
Resource for visually impaired people	36	18
Parent/guardian	29	14
Unknown	33	16
Laterality		
Bilateral	174	85
Unilateral	30	15

6 weeks' gestation, and the triplet pregnancy had been electively reduced to a singleton pregnancy at 10 weeks' gestation. Preterm birth and LBW both occurred in 25% of multiple births. In singletons, 11% and 9% were born preterm and LBW, respectively; these estimates are similar to normative data (p = 0.37 and p = 0.092, respectively).

Maternal age at birth in the overall cohort (23.5 ± 6 years; p < 0.001, one-sample *t*-test) was significantly lower than in the general population (27.2 years; p < 0.001). Compared with the general population, our sample included a higher proportion of mothers aged < 25 years (66% versus 27%; p < 0.001) and fewer mothers aged > 30 years (14% versus 36%; p < 0.001). Maternal age in primaparous women (22 ± 5 years) remained significantly lower (p < 0.001) than in primaparous women in the general population (24.9 years).

The proportion of primaparous women (76%) in this cohort was significantly higher (p < 0.001) than in the general population overall and across maternal age groups up to 30 years of age (Table 4).

A prior pregnancy was reported in 46% (87/189) of cases, of which 53% (46) resulted in a live birth. A history of a spontaneous or induced termination was noted in 38% of cases (65/171).

Table 3. Infant and maternal characteristics at birth.

Category (n*)	n	%	2000 Birth data (%)	p-value
Singleton (n = 204)	196	96	97	0.422
Birthweight (n = 198)				
VLBW (< 1500 g)	1	1	1	0.282
LBW (1501–2500 g)	18	9	6	
NBW (2501–4000 g)	168	85	82	
HBW (> 4000 g)	11	6	10	
Gestation (n = 198)				
< 32 weeks	2	1	2	0.912
32–36 weeks	20	10	10	
37–42 weeks	171	86		
> 42 weeks	5	3		
SGA (n = 198)	6	3		
Caesarean delivery (n = 183)	55	30	23	0.027
Mother's age at birth (n = 196)				
< 20 years	58	30	12	
20–24 years	71	36	25	
25–29 years	41	21	27	
30–34 years	16	8	23	
35–39 years	7	4	11	
> 40 years	3	2	2	
Parity (n = 189)				
0	143	76	40	< 0.001
1	32	17	32	
2	13	7	17	
3	1	1	6	

* Sample denominator varies based on availability of information and is presented in parenthesis.
VLBW = very low birthweight; LBW = low birthweight; NBW = normal birthweight; HBW = high birthweight; SGA = small for gestational age.

Table 4. Frequency of primaparity (n = 188).

Age category, years	Primaparity (%)		
	Optic nerve hypoplasia	National	p-value
< 20	96	79	< 0.001
20–24	80	46	< 0.001
25–29	59	36	< 0.001
30–34	50	29	0.14
35–39	57	22	0.05
> 40	0	21	0.07

Birth complications

Delivery complications were recorded in 39 cases (19%). Fetal distress occurred in 8% (17/204) and was significantly more frequent than in the general population (4%; p = 0.003). Eight cases were breech at delivery. The use of instruments (suction, vacuum, forceps) was necessary in the delivery of 13 cases (6%), which is comparable with the 7% in the general population (p = 0.89). Six cases required emergency caesarean delivery; inciting factors were fetal distress (three cases), nuchal cord (one case), placental abruption (one case) and unknown (one case). Other complications at delivery included three reports of increased maternal body temperature.

Documentation of neonatal complications was found in 62% (127/204) of cases; the most common were jaundice (93 cases), hypoglycaemia (48 cases) and distress (40 cases). Temperature instability was found in 15 cases. Other documented neonatal complications included an infection in seven subjects and persistent pulmonary hypertension in one subject.

Prenatal history

Systematic maternal interviews were obtained for 55% (105/192) of cases, excluding adopted subjects. Compared with the rest of the cohort, the questionnaire sample was similar with regard to laterality of ONH (p = 0.11, Fisher's exact test), gender (p = 0.17), referral source (p = 0.45), birthweight (p = 0.40), gestational age (p = 0.54), and first births (p = 0.24). There was a predominance of White subjects (p < 0.001)

in the sample. Mothers participating in the questionnaire tended to be older (24.1 ± 6 years) than those in the remainder of the cohort (22.8 ± 6 years); however, the difference was not significant (p = 0.058, Wilcoxon rank-sum test).

Reproductive history

Mean maternal ages at menarche and sexual debut were 12.5 ± 1.7 years and 16.3 ± 2.3 years, respectively. A subgroup of 9% (8/85; 20 could not remember) of mothers reported abnormal menstrual cycles in the 6 months prior to conception. There was no history of birth defects in previous children of multiparous women.

A total of 36% of mothers reported using hormonal contraceptives in the year prior to conception and 10% (n = 11) had been using hormonal contraceptives when the index child was conceived.

Index pregnancy characteristics

Conception of the index child had been planned in 70% of cases. Nearly all (99%) mothers sought prenatal care. Overall, 87% initiated care in the first trimester and 2% in the third trimester. Prenatal vitamins were used in 93% of pregnancies. Prenatal vitamins were used in the first two trimesters (≥ 4 months) by 72% of mothers and by 60% for the entire pregnancy (8–9 months). Infertility treatment for conception had been used in three cases: two had had *in vitro* fertilization (one had used a donor egg) and one had undergone ovulation stimulation.

Prenatal complications

Gestational vaginal bleeding occurred in 33 cases (31%); the occurrence peaked in the second month of pregnancy (12%). Pregnancy was threatened by miscarriage in 17% of cases. The prevalence of anaemia during pregnancy was 31% and anaemia was detected equally (41%) in the first and second trimesters. Vaginal and urinary tract infections were reported in 31% and 30%, respectively, of pregnancies. Both types of infection occurred most often in the second trimester (52% and 70%, respectively).

Additional prenatal complications ascertained from study files (n = 204) indicated gestational diabetes in eight cases (4%) and pregnancy-related hypertension in 11 cases (5%). Premature labour was documented in 25 cases (12%); the trimester in which labour began prematurely was known in 22 cases: 9% of premature labours occurred in the first trimester, 68% in the second, and 23% in the third. Systemic prenatal infection(s) was found in eight cases, including varicella (one case), cytomegalovirus (CMV) (two cases), tuberculosis (one case), hepatitis B (one case), hepatitis C (one case), parvovirus (one case), rubella (one case), Lyme disease (one case), and sepsis caused by streptococcus B (one case).

Other miscellaneous complications identified from study files included oligohydramnios (one case), amniotic fluid leak (two cases), partial placental abruption (one case) in the second trimester, elevated α-fetoprotein levels (four cases), intra-uterine growth restriction (two cases), significant abdominal trauma (four cases), and a hunger strike during the fourth month of gestation. Significant abdominal trauma included multifetal reduction in the first trimester, gunshot wound in the third trimester, surgical removal of an ovarian tumour in the first trimester, and physical assault.

Maternal weight

Pre-pregnancy BMI was within normal limits in 62% of mothers and 22% were considered underweight (low BMI) at conception. A stratified analysis of weight gain by pre-pregnancy BMI (Table 5) indicated that nearly one-third (29%) of mothers gained below the recommended guidelines.

Weight loss during pregnancy was found in 48% of mothers; 31% (33/50) lost > 1.4 kg. Of mothers who lost > 1.4 kg, 82% had a low-to-normal pre-pregnancy BMI. A total of 91% of incidences of weight loss occurred in the first two trimesters. There were three reports of overall negative weight gain (final weight less than pre-pregnancy weight). These subjects had an above-normal (high) BMI before pregnancy and the total weight lost during pregnancy in each case was 7.7 kg, 14.1 kg and 18.1 kg.

Smoking, alcohol and recreational drug use

Approximately one-third (31%) of mothers reported a history of smoking before pregnancy and 58% (19/33) continued to smoke, to varying degrees, into the pregnancy. Smoking cessation was initiated by four mothers in the first month, seven in the second month and one each in the third and fourth months; six smoked during the entire pregnancy (4–10 cigarettes per week). Among non-smokers (82%; 86/105), 25% were exposed to second-hand smoke in the home.

Alcohol use at any time during pregnancy was reported by 33% of mothers. Any use of alcohol in the first trimester was reported by 28%: 22% in month 1; 12% in month 2, and 8% in month 3. Among those who consumed alcohol, two mothers drank (two drinks per week) habitually, one during the first trimester only and one throughout the pregnancy. There were no reports of excessive use of alcohol.

Table 6 presents frequency of use during pregnancy of various drugs. Vitamins or supplements other than prenatal formulations included iron (20 cases), calcium (three cases), folic acid (three cases), B-vitamins (one case), echinacea (one case), gingko biloba (one case), ω-3 fatty acid (one case) and cranberry extract (one case). Recreational drugs used during pregnancy included marijuana (11 cases), cocaine (one case), crack cocaine (one case) and LSD (four cases). There was no use of opiates.

Other drugs used during pregnancy in individual cases included antibiotic eyedrops (second trimester), heparin

Table 5. Pre-pregnancy body mass index and weight gain during pregnancy* (n = 105).

		Weight gain (%)		
Body mass index	n	Below normal range	Within normal range	Above normal range
Low (< 19.8)	23	35	52	13
Normal (19.8–26)	65	28	34	39
High (> 26)	17	24	24	53

* According to the Institute of Medicine (1990) guidelines of weight gain during pregnancy.

Table 6. Drug use during pregnancy (n = 105).

Drug category	n	%	Trimester of exposure[§]	
			1 tri	2 tri
Analgesics				
NSAID*	16	15	–	–
Acetaminophen	51	49	–	–
Narcotic	10	10	60%	70%
Vitamins (other than prenatal)	30	29	56%	84%
Antibiotics	39	37	28%	59%
Cough or cold	17	16	24%	24%
Antihistamine	14	13	54%	62%
Anti-nausea	7	7	71%	43%
Antacid and laxative	6	6	33%	66%
Diet	1	1	100%	–
Asthma	3	3	33%	33%
Anti-epileptic	0	0	–	–
Sedatives	7	7	71%	14%
Psychotropic[†]	5	5	60%	60%
Cortisone	7	7	71%	43%
Insulin	2	2	100%	100%
Thyroid	4	4	100%	100%
Retin-A	2	2	50%	50%
Hormonal contraceptives	11	10	100%	–
Fertility hormones[‡]	3	4	100%	–
Recreational drugs	16	15	100%	13%

* NSAID, non-steroidal anti-inflammatory drug.
[†] Psychiatric medications for treatment of depression, anxiety and attention-deficit hyperactive disorder.
[‡] Progesterone, oestrogen and lupron.
[§] The denominator is the total number of subjects reporting use of the respective drug. Frequency estimates are not mutually exclusive.

(trimester unknown), energy pills (first trimester) and desonide 5% (first and second trimesters). There were two reports of non-drug toxic exposures: to asbestos in the first trimester, and to liquid mercury in the first and second trimesters.

Family history

There were no familial cases of ONH. Twenty-two subjects had a family history of eye disease, with strabismus in seven cases, amblyopia in seven and isolated reports of other eye diseases in eight cases.

Educational attainment

In the questionnaire sample, 23% of mothers reported that they had received < 12 years of education and 60% had received > 12 years at the time of the birth. Maternal educational attainment was similar to that recorded in the general population ($p = 0.81$).

Discussion

Past research on ONH collectively produced a broad spectrum of factors as potential aetiological correlates; however, such implications often resulted from selective case samples, small sample sizes, isolated exposures, and/or were subject to the limitations imposed by incomplete data. The objective of this study was to characterize the perinatal and prenatal features of ONH to help verify or refute previous findings with data from a large, prospective cohort of patients.

The ONH cases described in this report comprised 81% of patient referrals for ONH to our ophthalmology clinic from across the USA since 1992, although a majority resided within southern California. The heterogeneous racial or ethnic distribution observed in this cohort offers a unique demographic illustration of the incidence of ONH beyond the homogeneous samples studied by lead researchers of ONH in Scandinavia. Although the racial or ethnic make-up of this cohort generally reflects that of the region, a possible predilection of White subjects to and protection of Hispanics and Asia-Pacific Islanders against ONH is suggested by comparison with the clinic's patient population. It is possible that subjects referred from outside southern California skew the racial or ethnic distribution in this cohort. Nonetheless, susceptibility to ONH cuts across racial and ethnic lines.

There was no evidence of heritability; family history was negative for ONH and there were no siblings affected by ONH (limited to cases with older siblings). Genetic linkage cannot be eliminated, however, as all twin births were dizygotic.

Similarly to previous research, we found a predominance of young maternal age and primaparity among cases of ONH. It is not clear from past studies whether primaparity is directly related to ONH or whether it just appears to be associated through young age, with age as the real issue (Margalith et al. 1984). The predominance of primaparity after stratification on maternal age (Table 4) found in our cohort can be added to previous evidence (Tornqvist et al. 2002) against this confounding hypothesis. The potential causal relationship of primaparity or younger maternal age with ONH remains unclear.

The birth characteristics of our patients were unremarkable, contradicting findings by Tornqvist et al. (2002) that preterm birth and LBW are, respectively, 3.5 and five times more likely in cases of ONH. This discordance in findings may be explained by the different inclusion criteria of the case-control study by Tornqvist et al. (2002). The frequency of preterm birth and LBW in our cohort did not vary by laterality of disease, maternal age or parity.

Complications at delivery were significant for an increased frequency of caesarean delivery and fetal distress. The justification for caesarean delivery was unknown in many cases and, therefore, contributing factors and relevance to ONH could not be evaluated. The most common neonatal complications were hypoglycaemia, jaundice, distress and temperature instability. Interestingly, neonatal distress affected bilateral and unilateral cases equally ($p = 0.46$), whereas fetal distress, jaundice and temperature instability occurred almost exclusively in bilateral cases. Bilateral cases were also more likely to have had a neonatal hypoglycaemic event (35% versus 12%), although this finding only approached

significance ($p = 0.058$). Fetal and neonatal complications in the presence of birth defects are not surprising; the correlation of perinatal complications with laterality of disease in cases of ONH, however, suggests that more severe embryopathy may increase the likelihood of perinatal complications.

Although the birth findings associated with ONH are important features of the disease, a better understanding of its aetiology is gained by focusing on prenatal characteristics. Prenatal complications implicated by previous research, including gestational diabetes, hypertension and viral infection, did not stand out as potential risk factors in our cohort. Gestational diabetes (4%) and pregnancy-related hypertension (5%) were similar in frequency to estimates from national birth data (3% [$p = 0.40$] and 4% [$p = 0.27$], respectively; Martin et al. 2002). Prenatal viral infections were present in too few numbers to support a suggested role in ONH pathogenicity. We did find two cases with prenatal CMV exposure. This finding, however, is non-significant when compared with published pregnancy infection rates of 2.0–2.2% ($p = 0.34$) (Stagno et al. 1986; Yow et al. 1988).

Interestingly, our study uncovered a high frequency of other prenatal complications not previously discussed in the literature, including, specifically, premature labour and gestational vaginal bleeding. Early onset of labour was six times more common than in the general population (2%; $p < 0.001$) (Martin et al. 2002), occurred more frequently in the second trimester, and was equally present in unilateral and bilateral cases ($p = 0.70$). Less than one-third of pregnancies with premature labour resulted in preterm birth.

The prevalence of gestational vaginal bleeding (33%) exceeded population estimates (up to 22%; $p = 0.025$) (Ananth & Savitz 1994). Reports of vaginal bleeding were more common in the first trimester (64%) and the remaining cases were equally distributed between the second and third trimesters. Timing of vaginal bleeding correlates with underlying complications, including: trophoblastic disease; spontaneous abortion and threatened abortion when occurring early in gestation, and incompetent cervix and placental abnormalities when occurring in mid- and late pregnancy (Yang et al. 2005). Although the direct association with fetal development is unclear, an increased risk of congenital malformations has been suggested if vaginal bleeding is present early in gestation (Sipila et al. 1992; Ananth & Savitz 1994).

Pre-pregnancy BMI and weight gain during pregnancy are suggested to be associated with, among other things, available nutrient reserves and increases in fat and nutrient stores and plasma volume, respectively. Frequency of low weight gain in our cohort was dramatically higher ($p < 0.001$) compared with population data for low (35% versus 3.7%) and normal (28% versus 5.3%) pre-pregnancy BMI categories (Shieve et al. 2000). Another striking anthropometric finding was the high prevalence of weight loss, particularly in the first two trimesters. Hyperemesis gravidarum was not surveyed and, thus, its contribution to low weight gain could not be ascertained. This combination of hyperemesis with low weight gain has been found to increase the risk of adverse outcomes-associated fetal growth (Dodds et al. 2006). Low weight gain affected all maternal age groups equally. Weight loss, however, tended to occur in younger mothers (22 years compared with 26 years; $p = 0.002$). The role of weight gain and prenatal nutrition as a potential contributing factor to the development of ONH requires further consideration.

Exposure to smoking, alcohol and recreational drug use in our cohort was isolated, contradicting the numerous reports of these factors as aetiological correlates of ONH. Figures for smoking during pregnancy are poorly estimated in the national birth data; however, when compared with population-based data on pregnant women (Shieve et al. 2000), our finding that 18% (versus 33%) of mothers had smoked at any time during pregnancy was actually low ($p = 0.001$). Excessive use of alcohol prenatally was not evidenced in any of the cases with detailed histories. Similarly, Tornqvist et al. (2002) found no association with alcohol consumption, although this was not systematically studied.

This study has a number of strengths, including its large sample size, near-consecutive ascertainment of cases from a diverse referral base, uniform diagnostic criteria, and systematic assessment of prenatal history. Inclusion of cases was not based on disease severity or laterality. Recent evidence that additional features of the disease are independent of laterality supports such broad inclusion criteria (Garcia-Filion et al. 2008). The unique contributions of our study are the demographic and birth characteristics of a large cohort of patients with ONH and comprehensive prenatal assessment. Non-participation in the study by 19% of eligible patients with ONH was probably non-systematic, making the exclusion of their information an unlikely source of bias. Nearly half the cohort had not undergone systematic prenatal assessments, which may cause some information bias; however, the comparability of the sample subset with the cohort on several key features minimizes this threat. Prenatal assessments are also subject to recall bias. A standard protocol for conducting maternal interviews was employed to improve the accuracy of exposure estimates. Other limitations to the data include the absence of a control group and the collection of birth characteristics from study file documentation rather than through a systematic questionnaire. The latter limitation may lead to an underestimation of perinatal complications as documentation may be incomplete, and an overestimation of complications associated with disease laterality as a result of the increased likelihood that adverse events would be more frequently recalled in more severely affected cases.

Optic nerve hypoplasia is well recognized as a disease that occurs with increasing frequency. Although the pathogenic factors of ONH remain largely unknown, some features persist, especially young maternal age and primaparity. Our findings challenge many of the other factors previously suggested and introduce new, potentially significant prenatal characteristics that warrant study under more stringent methods and include: premature labour; gestational vaginal bleeding; low weight gain, and weight loss during pregnancy. Strong epidemiological investigations into ONH are necessary, involving thorough, systematic assessment of prenatal characteristics and the use of a control

group to enable accurate evaluation of risk factors.

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