Prenatal Factors in Infantile Strabismus

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ABSTRACT

Purpose:

To identify any common prenatal maternal factors influencing pregnancy that may predispose infants to develop infantile strabismus.

Methods:

A case control study was designed to evaluate the risk factors for strabismus. A set of exclusion and inclusion criteria was established for the cases and controls. The participating practices included fourteen private practices and three public hospitals throughout Victoria. Infants with infantile strabismus were recruited to the study on a voluntary basis as they presented to the various ophthalmic practices and hospitals. The control group participants were obtained from five Maternal and Child Health Centres. The mothers of the infants were given a pilot-tested questionnaire to complete. The questionnaire was made up of general questions relating to the mother and infant, 'masked' questions and specific questions related to the usage of alcohol, drugs and tobacco by the mother during pregnancy.

Results:

This study included 43 infants with strabismus and 100 controls. The strabismus group consisted of 37 cases of infantile esotropia and 6 cases of infantile exotropia. There were no known neurological deficits in either group. All infants were less than 12 months of age. There were several significant differences between the two groups. The most significant finding was that of parity, with 19% of infants in the strabismus group being the mother's first born, while in the control group 51% of infants were the mother's first born ($c_{-} = 13.0$, df = 1, p = 0.0003). More mothers from the strabismus group took medication prior to pregnancy compared with the control group, the incidence being 14% and 5% respectively ($c_{-} = 3.57$, df = 1, p = 0.06). More of the mothers in the strabismus group (63%) had a history of ever smoking (that is, past or current smoker) compared to the control group (47%) ($c_{-} = 3.00$, df = 1, p = 0.08) and more lived with a partner who smoked (40%) compared to the control group (22%) ($c_{-} = 4.4$, df = 1, p = 0.04). Strabismus in infants was not significantly associated with a family history of strabismus (p > 0.05).

Conclusion:

In this study, it appears that exogenous factors such as maternal smoking and medication usage, as opposed to endogenous factors, such as maternal and family ocular history and maternal medical conditions present prior to and during pregnancy, may have been more prominent factors in the development of infantile strabismus.

Key words: esotropia, exotropia, pregnancy, alcohol, smoking, drugs.

INTRODUCTION

Numerous theories exist as to the aetiology of some of the different types of strabismus, however the cause of early onset strabismus remains unclear. Some of the earlier theories which have been postulated include a faulty fusion faculty,[1] abnormal binocular reflexes,[2,3,4] hereditary or genetic factors,[5,6,7,8,9] birth complications and trauma,[9,10,11] viruses such as measles or whooping cough,[5,12,13] anatomical anomalies[12] and neurological problems.[10,14] Other associated findings include cortical damage or anomalies,[15,16] prematurity and low birth weight infants.[17,18,19]

The prevalence of infantile strabismus in the general population has been estimated to be between 0.1% and 2%[6,13,16,20,21] and between 13% and 60% in the mild to severe neurologically impaired population.[10,11,22,23,24,25] This finding suggests that central nervous system damage or involvement must play some role in the development of strabismus. Infants included in this study had no known general health or neurological problems, but may have had some subtle undetectable central nervous system dysfunction that could account for the development of strabismus.[15,20]

It has been hypothesised that early abnormal development of the visuomotor system and the influence of prenatal factors, particularly in the area of environmental and toxic effects, appear to indicate some causal relationship with strabismus. Prenatal toxic risk factors for the development of strabismus have shown an association with alcohol intake[25,26,27] tobacco smoking[28,29,30] and drug usage[28,31,32,33] during pregnancy. These studies however differ in many aspects, making a definite causal relationship difficult to determine, with some authors choosing to study one variable, while others have looked at the effects caused by multiple variables.

The aim of this research was to study the mothers of infants with infantile strabismus in order to compare prenatal factors in a strabismic population with a 'normal' control population.

METHOD

Two groups of infants were involved in this study, a group with strabismus and a control group without a strabismus. Ophthalmic practices and major public hospitals throughout Victoria were approached to recruit the strabismus group. They included 14 private practices and three hospitals (the Royal Children's Hospital, the Royal Victorian Eye and Ear Hospital and the Geelong Hospital). The control group participants were from five Maternal and Child Health Centres from the Geelong

region. Ethics approval was sought and obtained from all three public hospitals and from the La Trobe University Human Ethics Committee.

A set of exclusion and inclusion criteria was established for each group of subjects. All the infants in both groups were less than 12 months of age. Infants were excluded from both groups if there was any known neurological problem, if they were born at less than 36 weeks gestation or if they had a birth weight of less than 2500 grams. All the infants in the strabismus group had infantile strabismus, which had appeared during the first 6 months of life and was not the result of any underlying ocular or systemic condition. All the infants in the control group had no evidence of strabismus.

A specially designed pilot-tested questionnaire was used to collect data for this study. The questionnaire was designed with three main types of questions. First, a group of general questions related to the mother and her personal particulars such as age, weight and nationality. Second, a group of specific questions related to the mother and infant, such as the infant's gender, gestational age and birth weight, birth history including delivery type, current and/or prior birth complications as well as the planning of the pregnancy. Questions regarding eye problems in the mother or the immediate maternal and paternal family were included. Maternal medical history prior to or during pregnancy and subsequently, medications taken prior to and during pregnancy were noted. The tobacco smoking history of the mother and her partner and the alcohol and drug usage history of the mother formed part of this section of questions. The third group of questions included were 'masked' questions. These were included to reduce the perceived emphasis of the outlined relevant questions and included such topics as tea and coffee intake, regularity of exercise and working history during pregnancy.

Identical questionnaires and instructions were given to both groups. Participants were instructed to answer all the questions after reading and completing the Informed Consent form. Once written consent was obtained from the mothers, the infants were examined. The tests performed on both groups of infants, included corneal light reflex test, near cover test, ocular movements and a 20 dioptre prism reflex test. An approximate assessment of visual function was obtained, where possible using '100s & 1000s' and/or 'smartie' test placed at approximately 20 centimetres from the infant's face. The presence or absence of amblyopia was assessed by noting any objection or not to cover of either eye. Direct and consensual pupil responses were observed. The participants in the strabismus group also underwent cycloplegic refraction by an ophthalmologist in order to complete a full ophthalmic examination.

The statistical analysis package used in this study was SPSS for windows, version 6.1. Univariant analysis of the results was performed first for each variable using t-test for continuous data, Pearson's Chi-square and Fisher's exact test for categorical data. Following this, any significant finding(s), which included all factors with $p < 0.10$, were further analysed, in order to assess association between groups, using multivariant analysis - Odds Ratio (OR) with 95% confidence intervals (CIs). Backwards logistic regression was used to determine the final significant independent risk factors for strabismus at $p < 0.05$.

RESULTS

The strabismus group consisted of 43 infants with strabismus and the control group consisted of 100 infants without strabismus. The strabismus group consisted of 37 cases of infantile esotropia and 6 cases of infantile exotropia. The characteristics of the infants and their mothers are listed in Table 1.

For family history, the mothers were questioned regarding any history of eye problems, rather than a specific question on strabismus. The strabismus information was then extracted from the data. No mothers from the strabismus group and only one mother from the control group reported strabismus. The 21% incidence of strabismus reported among family members of the strabismus group was higher than the control group (11%) but not significantly different (see Table 2).

In the strabismus group, only 8 infants were the mother's first born (19%), while in the control group 51 infants were the mother's first born (51%), a statistically significant difference between the groups (see Table 2). Using multivariant analysis to control for 'ever smoked', 'live with smoker', medical condition prior to pregnancy and medication prior to pregnancy, this remained statistically significant with an Odds Ratio value of 4.83. Table 2 provides a summary of the independent risk factors analysed in this study and Table 3 shows the multivariant analysis of the independent risk factors.

In the strabismus group, medical conditions in the mothers prior to pregnancy were reported more frequently with an incidence of 19%, while the incidence in the control group was 8%, a borderline significant difference between the two groups (see Table 4). Medical conditions during pregnancy however were similar in each group (see Table 2).

More mothers from the strabismus group took medication prior to pregnancy compared with the control group (see Table 4), the incidence being 14% and 5% respectively, which was a borderline significant difference between the two groups. Using multivariant analysis to control for 'ever smoked', 'live with smoker', parity and medical condition prior to pregnancy, the Odds Ratio (OR) for medication taken prior to pregnancy for the groups was found to be statistically significant with a value of 4.1.

More of the mothers in the strabismus group (63%) had a history of ever smoking (that is, past or current smoker) compared to the control group (47%), which proved to be a borderline significant finding. This was statistically significant using multivariant analysis to control for 'live with smoker', parity, medical condition prior to pregnancy and medication prior to pregnancy. A statistically significant finding between the two groups was that more of the mothers of infants from the strabismus group (40%) lived with a partner who smoked compared to the control group (22%). The majority of these partners smoked indoors as opposed to outdoors. In the strabismus group the incidence was 26% compared with 11% in the control group, which was a borderline significant difference between the two groups. The type of smoker that the mother's partner was reported as included non-smoker, light, moderate or heavy smoker. This was defined by the mothers. In the strabismus group more partners were moderate (28%) or heavy (7%) smokers compared to the control group (11%, 2%, respectively), which was a statistically significant difference. The smoking behaviours of the mothers during pregnancy are shown in Figure 1.

Table 1. Infant and maternal characteristics

Risk factors	Strabismus cases n (%)	mean (SD)	Control cases n (%)	mean (SD)	t-test	p-value
Child birth weight	43(100)	3.51(0.66)	100(100)	3.45(0.52)	0.47	0.64
Child gestation	43(100)	38.9(1.83)	100(100)	39.2(1.40)	-1.15	0.26
Maternal age	43(100)	30.9(4.27)	100(100)	30.5(4.43)	0.54	0.59
Pre-pregnancy weight	39(90.7)	66.7(12.66)	99(99)	65.7(9.24)	0.48	0.64
Child's age at presentation	43(100)	6.72(2.21)	100(100)	7.68(2.06)	-2.42	0.018

Table 2. Summary of risk factors and univariant analysis

Risk factors	Cases=43 n (%)	Controls=100 n (%)c_	Pearson's Chi-square	p-value	df
Gender of infant					
- male	18 (42)	50 (50)	0.80	0.37	1
- female	25 (58)	50 (50)			
Exercise	33 (77)	76 (76)	0.62	0.73	2
Coffee	25 (58)	60 (60)	0.04	0.84	1
Tea	28 (65)	65 (65)	0.0002	0.99	1
Strabismus					
- self	0 (0)	1 (1)			
- family	9 (21)	11 (11)	2.47	0.12	1
Birth complications	12 (28)	21 (21)	0.81	0.37	1
Planned pregnancy	35 (81)	81 (81)	0.003	0.96	1
Lifestyle change	16(37)	30 (30)	0.72	0.4	1
Parity	8 (19)	51 (51)	13.00	0.0003*	1
Medical condition					
- prior	8 (19)	8 (8)		0.08+±	
- during	16 (37)	38 (38)	0.04	0.84	
Medications					
- prior	6 (14)	5 (5)	3.57	0.06±	1
- during	34 (79)	72 (72)	0.42	0.52	1
Consumption of alcohol					
- first trimester	18 (42)	53 (53)	1.49	0.22	1
- second trimester	14 (33)	33 (33)	0.001	0.97	1
- third trimester	17 (40)	44 (44)	0.25	0.62	1
Ever smoked - mother	27 (63)	47 (47)	3.00	0.08±	1
Smoked					
- first trimester	13 (30)	21 (21)	1.41	0.23	1
- second trimester	8 (19)	14 (14)	0.58	0.45	1
- third trimester	8 (19)	15 (15)	0.36	0.55	1
Mother lived with smoker	17 (40)	22 (22)	4.36	0.04*	1
Where partner smoked					
- outdoors	6 (14)	11 (11)			
- indoors	11 (26)	11 (11)	5.34	0.07±	2
Partners smoking type					
- light	2 (5)	9 (9)	-	-	-
- moderate	12 (28)	11 (11)	9.15	0.03*	3
- heavy	3 (7)	2 (2)			

Fisher's exact test result
* significant at $p < 0.05$
± borderline significance at $p < 1.0$

Table 3. Multivariant analysis

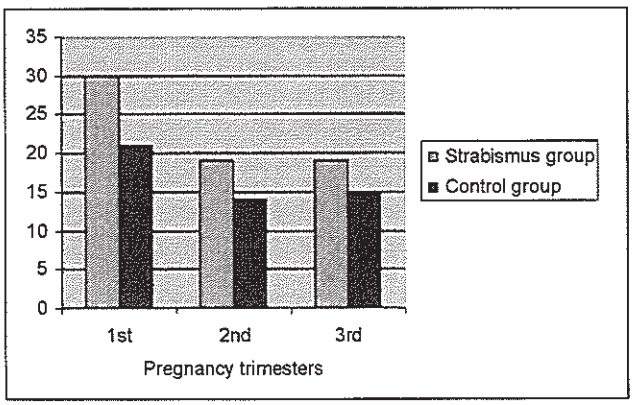
Risk factors	Strabismus cases N=43 n (%)	Controls N=100 n (%)	Odds Ratio (OR)	95% Confidence Intervals
Ever smoked	2 7(63)	47 (47)	2.7	1.19, 6.03
Medication -prior	6 (14)	5 (5)	4.1	1.06, 16.13
Parity	8 (19)	51 (51)	4.83	1.96, 11.88

Table 4. Medical conditions and medication taken prior to pregnancy for the strabismus and control groups

Medical conditions prior to pregnancy	Strabismus group N = 43	Medication taken	Control group N = 100	Medication taken
Asthma	1	1	1	2
Depression	1	1	1	1
Schizophrenia	1	1	-	-
Diabetes	1	1	-	-
Migraine	1	1	-	-
Rhinitis	1	1	-	-
Thyroid disease	1	1	-	-
Heroin addiction	1	1	-	-
Hypertension	-	-	2	2
Heart problems	-	-	1	-
Anaemia	-	-	1	1
Thalassemia minor	-	-	1	-
Addison's disease	-	-	1	-

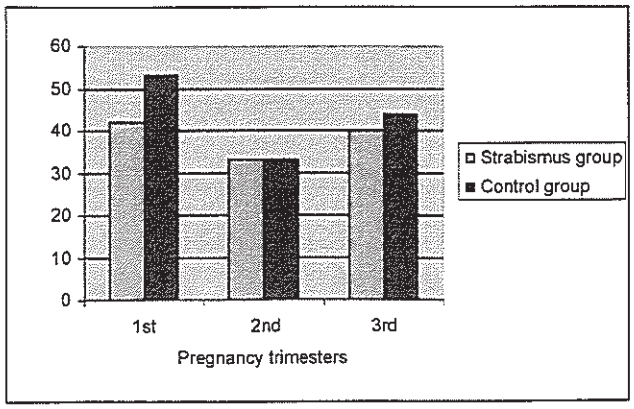
+ not mutually exclusive, some mothers in strabismus group used multiple medications

Figure 1. Cigarette smoking behaviours during pregnancy



Alcohol consumption patterns over each of the three trimesters of pregnancy were similar between the two groups (see Table 2). A trend noted in both groups was that the consumption of alcohol decreased during the second trimester, increasing again in the last trimester but not to the level of that in the first trimester (see Figure 2).

Figure 2. Alcohol consumption behaviours during pregnancy



DISCUSSION

The results of the present study suggest that exogenous factors such as maternal active and passive smoking and medication usage may have been more prominent factors in the development of strabismus among some of the infants, as these activities undertaken specifically during pregnancy were the only maternal underlying difference between the strabismus and control groups. As there was only one mother who reported a history of strabismus, it seems that maternal and family history was not a direct contributing factor for development of strabismus in this group, in contrast to other studies.[5,6,7,8,9]

An interesting and significant finding was that of parity, with only 19% of the infants with strabismus being first born, compared to 51% in the control group. This finding indicates that there is an increased incidence of a mother's infant developing strabismus after the first pregnancy. This has also been reported among studies of abnormal pregnancy outcome[38] and among studies of children with Fetal Alcohol Syndrome (FAS),[26,39,40] where there is an increased risk with subsequent pregnancies. Of the studies which reported parity as a possible risk factor for strabismus, no specific explanations were provided. Chew et al.[29] reported that parity was significant for esotropia. In contrast, Graham[41] and Podgor et al.[42] reported no relationship between the incidence of strabismus and the number of or positioning of siblings in a family.

Maternal age is an important factor to consider, as this would be expected to increase with the number of children. However, in this study the mean age of the mothers was similar in the two groups, which would indicate that many of the mothers of the strabismus group had their first child at a younger age. The control group therefore consisted of a higher proportion of older first-time mothers where perceptions of behaviours such as smoking, alcohol consumption and taking medications may have differed from younger first-time mothers. One limitation of the study that may influence parity was that the control group were from Maternal and Child Health Centres, where there is a higher attendance of first-time mothers. However, this would not explain the low incidence of first-born children with strabismus in comparison to the population. According to the Department of Human Services,[43] approximately 41% of infants were first-borns in 1999/2000. In the light of previous studies, further investigation is suggested to confirm this finding.

Medical conditions present prior to pregnancy occurred more frequently among the mothers in the strabismus group

compared with the mothers of the control group. Most of the conditions experienced by the mothers from both groups were chronic problems unrelated to pregnancy. No studies were found in the literature that looked at medical conditions present in the mother prior to pregnancy and the subsequent development of strabismus among their infants. Medical conditions during pregnancy occurred with almost equal incidence between the two groups.

In this study a significant difference between the groups revealed that it was more likely that the mothers from the strabismus group took medication prior to pregnancy as compared to the mothers of the control group. Strabismus as a consequence may be a result of medications taken prior to the knowledge of pregnancy when the mother's body was undergoing physiological change and adapting to pregnancy. This in turn may have resulted in changes to the properties of the different medications and also changes in the ability to control some of the medical conditions. Other influencing factors may have included the medical condition present, the range of medications taken and the small numbers of mothers that took medication in both groups. Medications taken during pregnancy however were not significantly different between the groups.

An association between strabismus and psychoactive drugs has been reported in previous studies.[31,32,33] Infantile exotropia has been reported as a common finding in infants with prenatal drug exposure.[31] In the present study, of the six infants with exotropia, there were three mothers who took medications; one antidepressants, one antipsychotics and the other methadone. These types of medications were not used by any of the mothers of infants with esotropia. However, one mother did use marijuana prior to her knowledge of pregnancy, giving birth to twins, one with esotropia. The reported effects of marijuana during pregnancy are inconsistent, with no convincing evidence to suggest smoking marijuana is harmful or teratogenic to humans or the fetus.[33,34,35,36] Methadone usage and the development of strabismus have been found to be associated in some studies.[32,37]

Both active and passive maternal smoking behaviours were found to be significantly different factors between the mothers from both groups. Of these, more of the mothers in the strabismus group were past or current smokers and/or lived with partners that generally smoked indoors. It is therefore possible that some of the infants during pregnancy may have been exposed to the effects of smoke directly via the mother smoking and/or passively via her partner.

The present study found that the majority of mothers from both groups smoked less than 15 cigarettes per day and so were classified as light smokers, as defined by other studies,[30,44] so a dose-response relationship with strabismus was not able to be established. There are conflicting reports on the dose-response relationship between smoking and strabismus, with one study reporting no relationship[30] and others finding heavy smokers, that is greater then 20 cigarettes per day, had a higher risk of congenital anomalies, including strabismus.[29,44]

Two of the six mothers of infants with exotropia smoked throughout pregnancy compared to only six of 37 mothers with infants with esotropia. Among women who smoked throughout pregnancy, an increased and statistically significant risk for esotropia has been reported[29,30] and an increased, but insignificant, risk for exotropia.[29]

In the present study, the higher incidence of the mothers' partners smoking in the strabismus group could have been an influencing factor in the development of strabismus. Of importance also is the finding that more of the mothers' partners from the strabismus group were moderate or heavy smokers, compared to the control group. This indicates possibly a greater risk of development of strabismus caused by the effects of passive smoking than the mother smoking.[45] The effects of paternal smoking and its passive smoking effects have been reported in the literature, with infants having lower birth weights and a higher risk of perinatal mortality.[46] Hakim and Tielsch[30] were the only researchers who looked at mothers exposed to secondary smoke via their partners and reported an increased risk of strabismus particularly esotropia, only when the mother smoked during pregnancy, but not if she was a non-smoker. It is still to be established whether abnormal outcomes are due to the pregnant mother's passive smoking or from direct damage to the paternal gene or sperm.[46] In conclusion, the fetus appears to be a passive smoker whether the mother or those around her smoke during pregnancy, which has detrimental consequences to development and health.[47,48]

In the present study the small numbers meant that it was not possible to further divide those who lived with partners who smoked into smoking and non-smoking mothers. Further investigation of passive smoking behaviours during pregnancy, whether in addition to active smoking or alone, would assist in further understanding this issue.

Alcohol consumption behaviours during pregnancy were similar in the mothers from both groups with no mothers consuming alcohol in large quantities or at 'at-risk' levels as defined by the Alcohol and Drug Foundation. In this study there were generally low levels of alcohol, smoking and medication usage by the mothers. Some mothers were multiple or concurrent users of these, all of which in high doses are known to be harmful to the fetus, making it difficult to attribute adverse effects to a single substance.

As all the questionnaire information concerning maternal and paternal behaviours was self-reported information after the infants were born, errors of under-reporting and recall bias may have occurred. Further studies involving test-retest reliability could clarify this result.

The findings of this study, particularly in relation to maternal behaviours and parity, suggest several possibilities. Known teratogenic behaviours such as smoking, consumption of alcohol and the taking of medication, undertaken by mothers both prior to and during pregnancy may affect the mother's body over a long period of time. The effects of these teratogens as a consequence may accumulate within the mother's system causing both physiological and genetic changes. These changes may have detrimental effects on the infants, the outcome or symptoms of which may remain relatively undetected in an initial pregnancy, but manifesting in subsequent pregnancies. Although these infants may not have major congenital malformations, they may present with minor abnormalities, including strabismus. What these changes are and how they produce these outcomes or consequences require further investigation. Paternal behaviours may also need to be addressed when considering conception and pregnancy outcomes in the future.

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