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Ophthalmologic follow-up of premature twins and triplets

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PURPOSE. To assess the influence of multiple gestation on the visual apparatus and on the general state of health of premature infants and to investigate the condition of the twin or triplet with the lowest birth weight compared to multiple gestation siblings.

METHODS. Seventy-seven premature twins or triplets (8 to 54 months of age) were monitored at the Verona University Ophthalmology Department from November 1995 to November 1999. In another 12 subjects (younger than 8 months), only the neonatal disease records were examined; these subjects were excluded from the ophthalmologic follow-up because they were too young to be tested reliably. The study sample was compared with 120 premature singletons monitored from January 1996 to March 1998. Visual acuity, ocular motility, strabismus, refraction defects, dioptric media, and fundus oculi were assessed.

RESULTS. The incidence of retinopathy of prematurity, refraction defects, or strabismus was not significantly different between premature twins or triplets and premature singletons. The twin or triplet with the lowest birth weight was more frequently affected by eye morbidity and the diseases typical of prematurity. This difference, however, was not statistically significant.

CONCLUSIONS. Premature infants are at a disadvantage compared to those born at term, irrespective of multiple birth status; multiple gestation adds no risk beyond that due to prematurity. (Eur J Ophthalmol 2003; 13: 439-44)

KEY WORDS. Twins, Prematurity, Myopia, Retinopathy of prematurity, Strabismus

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INTRODUCTION

There has been a substantial increase in multiple gestation births since the 1970s (1, 2). This trend might be due in part to the recent tendency to postpone the first pregnancy and the widespread use of fertility-stimulating therapies and assisted reproduction techniques, particularly in women over the age of 35. Multiple births occur more often in mothers of higher than average age at the first pregnancy.

Multiple gestation is associated with a greater risk of prematurity and a consequent increase in perinatal mortality and morbidity rates. Nevertheless, substantial progress in neonatal intensive care over the past few decades has led to marked improvement in survival rates among premature infants, facilitating the survival even of babies with very low gestational age and birth weight.

Prematurity and low birth weight, particularly pregnancies with duration of less than 30 weeks and a very low birth weight (VLBW) (less than 1500 g), are associated with a greater incidence of ophthalmologic disorders (3-9). Retinopathy of prematurity (ROP), refraction defects, and ocular motility deficiencies are

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very common problems in premature infants.

The aims of the present study were to evaluate the influence, if any, of multiple gestation on refraction, motility, and the incidence of eye disorders in premature children and to investigate, within each pair of twins or set of triplets, the condition of the twin or triplet with the lowest birth weight compared to twin or triplet siblings.

METHODS

We conducted a retrospective analysis of the clinical files of premature children monitored at our ophthalmology Department from November 1995 to November 1999, identifying a total of 89 multiple gestation premature children. Twelve subjects younger than 8 months were excluded from the ophthalmologic follow-up because they were too young to be tested reliably.

The ophthalmologic follow-up population was then subdivided into four age groups of approximately 1 year each: Group 1 (n = 67), 8 to 18 months; Group 2 (n = 41), 19 to 30 months; Group 3 (n = 27), 31 to 42 months; Group 4 (n = 14), 43 to 54 months. Some but not all infants have been followed repetitively in the various groups. The parameters analyzed were visual acuity, refraction defects, ocular motility, strabismus, and fundus oculi.

Refraction defects were assessed by cycloplegic videorefractometry (CVR) and cycloplegic autorefractometry (CAR); cycloplegia was obtained using cyclopentolate. We established that spherical equivalents –1.50 D or greater and +3.00 D or greater define myopia and hyperopia, respectively; a spherical equivalent difference of more than ±1.00 D between the two eyes defines anisometropia; and cylinder values of ±2.00 D or more define astigmatism. Strabismus was analyzed using manifest videorefractometry, the Hirschberg test, and the near and remote cover test.

The fundus was investigated in conditions of pharmacologic mydriasis (cyclopentolate) by indirect ophthalmoscopy without sedation. Only the posterior pole was assessed. All the subjects were previously submitted to fundus examination with scleral indentation up to regression of any ROP or to completion of the retinal vascularization.

Only one eye of each subject was included in the analysis. In cases in which there were discrepancies between the two eyes with regard to degree of ROP, visual acuity, ocular motility, or refraction defects, the most severely affected eye was included in the analysis.

We first compared the patients with a sample of 120 premature singletons studied in our department from January 1996 to March 1998, to establish whether multiple gestation has any effect on the visual apparatus or on the general state of health of the subjects. Unfortunately, the comparison between the two premature populations was possible only for the first two follow-up age groups, because no data were available for subjects beyond the age of 2 years in the premature singleton population. The second comparison was within the individual pairs of twins or sets of triplets, between the twin or triplet with the lowest birth weight and the corresponding twin or triplets of higher birth weight to identify the greater frequency, if any, of general and particularly ophthalmologic disorders in one or the other of the multiple gestation siblings.

The data were analyzed using the c2 test. A p value of less than 0.05 was regarded as statistically significant.

RESULTS

General characteristics of the cohort

Table I presents demographic characteristics of the cohort of multiple gestation children analyzed. The subjects in our sample were born at gestational ages ranging from 24 to 38 weeks (mean ± SD: 32 ± 3.14 weeks). Birth weights ranged from 540 to 2750 g (mean ± SD: 1625 ± 540.23 g).

The more serious the degree of prematurity or the lower the birth weight, the greater the frequency of neonatal disease and thus the need for neonatal intensive care measures such as mechanical ventilation and oxygen therapy. Infants with gestational age less than 32 weeks or who presented with VLBW more often had disease and, therefore, more often received intensive care than infants with gestational age equal to or greater than 32 weeks or with birth weight above 1500 g.

Of 89 subjects, 32% (29/89) presented with lung disease, particularly respiratory distress syndrome, but also bronchopulmonary dysplasia and hyaline membrane disease; 17% (15/89) had neurologic disorders

TABLE I - GENERAL CHARACTERISTICS OF THE STUDY POPULATION

General characteristics	Value
Place of birth	
Inborn	84
Outborn	5
Sex, n (%)	
M	46 (52)
F	43 (48)
Multiple births	
Twins	68
Triplets	21
Gestational age, wk, mean ± SD (range)	32 ± 3.14 (24-38)
Birth weight, g, mean ± SD (range)	1625 ± 540.23 (540-2750)
Mechanical ventilation, n (%)	
Yes	31 (35)
No	43 (48)
Not reported	15 (17)
Oxygen therapy, n (%)	
Yes	39 (44)
No	35 (39)
Not reported	15 (17)
Diseases associated with prematurity, n (%)	
Yes	38 (43%)
No	34 (38%)
Not reported	17 (19)

such as intraventricular hemorrhage and leukomalacia; 15% (13/89) had preterm anemia; and 13% (12/89) presented with heart disorders, particularly patency of Botallo duct.

Retinopathy of prematurity

85% (76/89) of the subjects did not develop ROP, 7% (6/89) developed stage 1 ROP, 4% (4/89) developed stage 2 ROP, and 1% (1/89) had laser-treated stage 3+ ROP. 2% (2/89) developed ROP of an unspecified stage, in that they came from another hospital and the ROP stage had not been assessed. 77% (10/13) of the subjects with ROP had gestational age less than 32 weeks and all belonged in the VLBW category. Statistical analysis showed a significant association between the development of ROP and premature birth ($p = 0.008$), low birth weight ($p = 0.002$), and oxygen therapy ($p = 0.003$).

Follow-up of premature twins/triplets from 8 to 18 months of age

Sixty-seven subjects between the ages of 8 and 18 months were included in Group 1. The parameters measured were refraction, motility, and fundus oculi.

Refraction. Myopia was detected in 3% (2/67), hyperopia in 4% (3/67), anisometropia in 3% (2/67), and astigmatism in 1% (1/67) of the subjects examined using CVR. At CAR myopia was detected in 3% (2/67),

hyperopia in 7% (5/67), anisometropia in 3% (2/67), and astigmatism in 1% (1/67).

Strabismus. Esophoria was present in 24% (16/67) of the subjects, exophoria in 12% (8/67), esotropia in 7% (5/67), and exotropia in 1% (1/67).

Fundus oculi. 12% (8/67) of the subjects presented with vascular tortuosity and 1% (1/67) ovalization of the optic disk. The subject with stage 3+ ROP underwent examination of the fundus under narcosis, during which we found, in addition to the aftermath of laser treatment, temporal optic disk pallor, traction of the temporal vascular arcades, a vitreoretinal traction area, and marked retinal pigment epithelial macular dystrophy.

Follow-up of premature twins/triplets from 19 to 30 months of age

Of the 67 subjects previously examined, 39 were included in Group 2. Two more subjects were entered into the study at this stage, so that Group 2 comprised a total of 41 subjects.

Refraction. CVR indicated that 5% (2/41) of the subjects had myopia and 2% (1/41) had hyperopia, whereas none of them presented with anisometropia or astigmatism. CAR generally confirmed the results of CVR, except in the case of hyperopia, which occurred in 7% (3/41) of the 41 subjects in Group 2.

Strabismus. Esophoria was present in 15% (6/41) of the subjects, whereas 12% (5/41) presented with exophoria, another 12% (5/41) with esotropia, and 2% (1/41) with exotropia.

Fundus oculi. 12% (5/41) of the subjects presented with vascular tortuosity and 2% (1/41) with ovalization of the optic disk. The status of the subject with stage 3+ ROP, who again underwent evaluation of the fundus under narcosis, remained unchanged compared to the previous observation.

Follow-up of premature twins/triplets from 31 to 42 months of age

Group 3 of our ophthalmologic follow-up population consisted of 27 subjects. Of these, 22 (81%) had undergone the previous monitoring examinations and 5 (18%) entered into the study at this stage. Of the 41 subjects in Group 2, 19 (46%) elected to discontinue participating in the study.

Refraction. CVR detected no cases of myopia, hyperopia, or anisometropia. 4% (1/27) of the subjects presented with astigmatism. CAR also detected no cases of myopia or anisometropia, whereas 7% (2/27) of the subjects were hyperopic and 18% (5/27) were astigmatic.

Strabismus. Exophoria was present in 41% (11/27) of the subjects, esophoria was present in 7% (2/27), and esotropia and exotropia were each present in 4% (1/27).

Fundus oculi. There was vascular tortuosity in 11% (3/27) of the subjects and ovalization of the optic disk in 4% (1/27). The subject with stage 3+ ROP did not take part in the follow-up beyond the age of 2 years.

Follow-up of premature twins/triplets from 43 to 54 months of age

Of the 27 subjects examined in the 31 to 42 month age bracket, 11 (41%) continued to take part in the follow-up. A set of triplets entered into the study at this stage, making a total of 14 subjects in Group 4.

Refraction. CVR, performed only in 14% (2/14) of the subjects in this age bracket, detected no cases of ametropia. CAR confirmed this result, with the exception of myopia and astigmatism, which were detected in 7% (1/14) and 36% (5/14) of the subjects, respectively.

Strabismus. In the near cover test, 86% (12/14) of the subjects presented with exophoria and 21% (3/14) with exotropia. There were no cases of convergent strabismus.

Fundus oculi. Only one subject (7%) presented with abnormalities of the fundus, a case of myopic retinopathy. The subject had entered into the study at this stage and was found to be myopic upon examination by CAR.

In all four age groups considered there was a statistically significant correlation between the presence of ametropias and low birth weight ($p = 0.017$); a history of neurologic disease ($p = 0.030$), particularly intraventricular hemorrhage; and ROP ($p = 0.001$). Subjects with ROP were more often affected by ametropias: 69% (9/13) of the ROP-positive subjects presented with ametropias and 23% (3/13) with emmetropias. Among the ametropias, those correlating most closely with ROP were myopia ($p = 0.001$) and anisometropia ($p = 0.001$).

Strabismus was also significantly associated with the risk factors considered (birth weight, p = 0.022; neurologic diseases, p = 0.039; ROP, p = 0.022); It was more frequent in subjects with ROP: 23% (3/13) of ROP-positive subjects presented with manifest strabismus and 15% (2/13) with orthophoria.

Comparison with premature singletons

Comparison of the results obtained in the cohort of twins and triplets with the population of premature singletons previously studied in our department revealed no significant difference in incidence or severity of ROP between the two premature populations. The frequencies of ametropia and strabismus were also comparable in premature twins and triplets and premature singletons.

Comparison between multiple-gestation siblings

Within each pair of twins or set of triplets, the twin or triplet with the lowest birth weight was invariably at a disadvantage compared to the sibling twin or triplets of higher birth weight, although the difference was not statistically significant. Morbidity associated with prematurity (p = 0.451), ROP (p = 0.328), ametropia (p = 0.679), strabismus (p = 0.802), and diseases of the fundus oculi (p = 0.281) were more frequent in the lower birth weight multiple gestation siblings.

DISCUSSION

Our data are consistent with a range of findings reported in the literature regarding the effects of prematurity on the visual apparatus and their implications (3-8, 10-18). Several studies report that prematurity and low birth weight are associated with a greater incidence of ophthalmologic disorders. In particular, VLBW premature infants constitute a high-risk population for the development of refraction defects, most notably myopia and ocular motility disorders (3-6). Prematurity and VLBW are also responsible for greater perinatal mortality and morbidity in twin pregnancies compared with singleton gestations (2). Multiple births have sometimes been seen as an additional risk for ocular sequelae, particularly for ROP, although not all studies have found this association. In 1956, for the first time, Kinsey (18) reported an increased risk of cicatricial ROP in multiple births. More recently, Bossi et al (19) found that twin gestation was a significant risk factor for ROP in multivariate statistics and, similarly, Schaffer et al (20) found an increased risk of reaching threshold ROP for twins compared with singletons. Others, such as Wolf et al (21), did not find this association. Blumenfeld et al (9) and Friling et al (22) noted no significant difference in the incidence of ROP between the twins and the singletons.

In the current study, we examined ocular morbidity in twin infants compared with premature singletons and found a similar incidence of ROP, ametropia, and strabismus between the single- and multiple-gestation populations. High grade prematurity and low birth weight, which are features shared by the two populations, are the main factors responsible for the development of ocular sequelae in prematurely born children, regardless of whether they were multiple gestation infants.

Consistent with other authors (3, 6, 14, 18), we found an association between neurologic conditions, particularly intraventricular hemorrhage, and ametropia or strabismus.

Prematurity, itself, with all the implications of shorter gestation, low birth weight, and greater incidence of morbidity, places both multiple gestation premature infants and premature singletons at a disadvantage compared to infants born at term. In conclusion, prematurity, not single or multiple gestation, is primarily responsible for the ophthalmic problems incurred in our infants.

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