Early Structural Status of the Eyes of Healthy Term Neonates Conceived by In Vitro Fertilization or Conceived Naturally

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PURPOSE. To evaluate the effects of in vitro fertilization (IVF) on early development of the eye in full-term healthy infants.

METHODS. A case-control study was performed. The study sample included full-term infants born from March 1 to August 14, 2006, in the Neonatal Department of Helen Schneider Women’s Hospital, Rabin Medical Center. Data were collected on sex, gestational age, birth weight, Apgar score, head circumference, body length, and mode of conception (IVF/natural). A full ophthalmologic examination was performed, including measurement of intraocular pressure, keratometry, ultrasound biometry, pachymetry, and funduscropy.

RESULTS. Sixty-six infants (132 eyes) were examined; 32 were conceived by IVF, and 34 were conceived naturally. Girls accounted for 56% of the IVF group and 44% of the natural conception group. There were no statistically significant differences between the groups in sex, gestational age, head circumference, intraocular pressure, axial length, anterior chamber depth, and lens thickness. The IVF infants had lower birth weight and body length than the infants born by natural conception (P = 0.052, t-test). Their keratometric and pachymetric values were also higher, but when birth weight and length were controlled, this difference remained statistically significant only for infants with a birth weight of less than 3000 g and a body length of less than 48.5 cm.

CONCLUSIONS. IVF apparently has no effect on early development of the eyes in full-term infants. The steeper corneal curvature and greater central corneal thickness in a subset of smaller IVF infants may reflect delayed corneal maturation. (Invest Ophthalmol Vis Sci. 2007;48:5454–5458) DOI:10.1167/iovs.07-0929

The population of infants conceived by assisted reproductive technologies (ART) has grown steadily in recent years. However, the prevalence of developmental abnormalities associated with ART remains largely unknown. Some studies reported higher rates of chromosomal aberrations and worse neonatal outcome in newborns conceived by in vitro fertilization (IVF) than newborns conceived naturally,1–3 whereas others noted no difference.4–9 Data on ocular outcome is even more limited. Antebly et al.,10 in a study of 47 infants conceived by IVF, found reduced visual acuity in 9%, anisometropia greater than 1.0 D in 17%, and major ocular malformations in 26%.

In a previous study,11 we investigated ocular growth in premature neonates conceived by IVF compared with those conceived naturally. We found no effect of IVF on early ocular growth, intraocular pressure, changes in corneal curvature, or retinal vascularization. Although our findings might have reflected a true similarity in ocular growth in infants conceived naturally and those conceived by IVF, we were concerned that the prematurity might have masked possible differences between the groups.

The purpose of the present study was to evaluate the effects of IVF on early development of the eyes in full-term healthy infants.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board of Rabin Medical Center and adhered to the tenets of the Declaration of Helsinki. Parents provided informed consent after receiving a detailed explanation of the nature of the study and its possible consequences.

Healthy, full-term infants born from March 1 to August 14, 2006, at the Neonatal Department of the Helen Schneider Women’s Hospital of Rabin Medical Center were eligible for the study. For the infants conceived by IVF, we performed ocular examination in those for whom parental consent was obtained; the parents refused in five cases. For the naturally conceived infants, we performed the examination at random in those for whom parental consent was obtained; parents refused in about half the cases. Family history of eye disease and the parents’ refractive errors were obtained.

Neonates from both groups who needed intensive care treatment or had medical, neurologic or ocular problems were excluded.

Data Collection

The records of every infant in the study were reviewed, and data were collected on gestational age, birth weight, Apgar score, head circumference at birth, and postconceptional age (PCA), in addition to type of conception (IVF or natural) and type of pregnancy (twin or singleton).

Ophthalmologic Examination

A single ophthalmologic examination was performed in each infant 36 to 72 hours after delivery. It included measurement of intraocular pressure (IOP), keratometry, ultrasound biometry, pachymetry, and funduscopy. The same ophthalmologist (ZH) performed all the examinations, and the same pediatric orthoptist/optometrist (IS) performed all the refraction measurements. The ophthalmologist was unmasked, and the pediatric orthoptist was masked as to the mode of conception of the examined infants.

IOP was measured (Tono-Pen; Solan, Jacksonville, FL) after instillation of two drops of topical anesthetic (oxybuprocaine HCl 0.4%; Fischer Pharmaceuticals, Tel Aviv, Israel). The eyelids were retracted.
Effects of IVF on Early Structure of Neonate Eyes

Sixty-six infants (33 boys, 33 girls; 132 eyes) were examined for the study. During the study period, no infant had to be excluded because of neurologic, medical, or ophthalmologic problems. Thirty-two infants, including four sets of twins (8 infants), were conceived by IVF, and 54 were conceived naturally. The IVF group had a female predominance (56%), and the natural conception group had a male predominance (50%). This difference was not statistically significant ($P = 0.325, \chi^2$ test).

Vaginal delivery was performed in 24 naturally conceived infants (70%) and 16 IVF infants (50%); the rest were born by cesarean section. This difference was not statistically significant ($P = 0.110, \chi^2$ test).

Gestational age, birth weight, head circumference, and body length in the two groups are presented in Table 1. Birth weight and body length were statistically significantly lower in the IVF group than in the natural conception group ($P = 0.032$ for both, $t$ test for two independent samples). The female infants had a significantly mean lower birth weight than the male infants in both groups (2925.3 g [SD ± 486 g] vs. 3247.4 g [SD ± 474.64 g], respectively in the whole cohort; $P = 0.015$, $t$ test for two independent samples).

Table 2 presents the oculor data of both groups. The horizontal and vertical corneal radii of curvature (R1/R2) were significantly smaller in the IVF group than in the natural conception group ($P = 0.003/0.017$ for the right eyes and $P = 0.015/0.012$ for the left eyes; $t$ test for two independent samples). However, when we controlled for birth weight and body length, the difference remained statistically significant only for neonates with a birth weight of less than 3000 g and a body length of less than 48.5 cm ($P = 0.019$ and $P = 0.04$, respectively; Mann-Whitney $U$ test).

Mean spherical equivalents of the right/left eyes were $+2.2D$ (SD ± 1.7)/$+2.0D$ (SD ± 1.9) in the IVF group and $+2.6D$ (SD ± 1.3)/$+2.5D$ (SD ± 1.4) in the natural conception group; the difference was not statistically significant. In addition, no statistically significant differences were found between the groups in axial length, anterior chamber depth, lens thickness, or IOP. Pachymetric values were significantly higher in the IVF group ($P = 0.075$ for the right eyes and $P = 0.047$ for the left eyes). However, when we controlled for birth weight and body length, the differences approached statistical significance ($P = 0.06$, Mann-Whitney $U$ test) only for the subgroup of infants weighing less than 3000 g, and it remained statistically significant ($P = 0.02$, Mann-Whitney $U$ test) only for the infants with a body length of up to 48.5 cm. The central corneal thickness measurements demonstrated more variability in the IVF group, as reflected by the different mean and median values. In the natural conception group, the mean and median central corneal thickness measurements were similar (Table 2).

In the whole cohort, as well as in each group separately, correlations were found for gestational age, birth weight, head circumference, and body length with corneal radius of curvature (negative correlations) and with axial length and anterior chamber depth (positive correlations; all $P$ values ranged between 0.0001 and 0.004; Pearson correlation). No correlations were found with spherical equivalent, lens thickness, central corneal thickness, and intraocular pressure. A statistically significant correlation was found in the whole cohort between myopia (neonates with spherical equivalent of less than $-1D$) and family history of myopia of more than $-1D$ ($P = 0.016, \chi^2$ test).

Retinal hemorrhages were found in six eyes of three infants in the IVF group and in five eyes of three naturally conceived infants, all of them after vaginal delivery. Retinal vascularization was normal in all infants.

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**Table 1. Perinatal and Morphometric Data in 66 Full-Term Infants Conceived Naturally or by IVF**

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>$t$</th>
<th>$P^*$</th>
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<tbody>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NC</td>
<td>33</td>
<td>38.8</td>
<td>1.3</td>
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<td>36.0</td>
<td>41.0</td>
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<td>38.5</td>
<td>0.9</td>
<td>38.0</td>
<td>37.0</td>
<td>40.0</td>
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<td>Birth weight (g)</td>
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<tr>
<td>NC</td>
<td>34</td>
<td>3214.5</td>
<td>466.1</td>
<td>3143.5</td>
<td>2530.0</td>
<td>4400.0</td>
<td>2.193</td>
<td>0.032</td>
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<td>IVF</td>
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<td>513.1</td>
<td>2862.5</td>
<td>2010.0</td>
<td>4150.0</td>
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<td>Head circumference (cm)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>NC</td>
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<td>1.2</td>
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<td>0.998</td>
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<td>36.5</td>
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<td>Body length (cm)</td>
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<tr>
<td>NC</td>
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<td>49.7</td>
<td>1.9</td>
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<td>46.0</td>
<td>55.0</td>
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<td>IVF</td>
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<td>44.0</td>
<td>53.0</td>
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Values in bold type are statistically significant. NC, natural conception; IVF, in vitro fertilization.

*P* values were derived from $t$ tests for two independent samples.
failed to find signs of neurologic impairment, malformations, or developmental delay during infancy and early childhood. In another study, 19% of the IVF infants showed minor developmental problems at 1 year, but by 2 years neuropsychological development was within normal range. A Danish study of 3438 twins conceived by IVF or intracytoplasmic sperm injection (ICSI) and 10,362 non-IVF twins reported that despite the higher discordance in birth weight and more intensive care unit admissions in the ART infants, neonatal outcome seemed to be comparable between the groups. These findings were supported by another twin study, of neurologic sequelae, showing no difference between children born after ICSI or after IVF.

To the best of our knowledge, information on normal biometric and refractive parameters in full-term healthy IVF infants has not been published to date. In our previous study of 135 premature neonates, we found that the biometric and IOP values, as well as retinal vascularization, did not differ between IVF infants and infants conceived naturally. However, these findings might have been biased by differences attributed to prematurity. For example, a previous oculometric study on preterm versus full-term infants demonstrated that in premature infants, 40-week adjusted axial lengths were shorter in infants with shorter gestational age. In preterm infants, more fetal anterior segment proportions, with flatter anterior chambers and thicker lenses, were found. Compared with the full-term infants, absence of the usual correlation between axial

### Table 2. Biometric, Refractive, Pachymetric, and IOP Data in 66 Neonates by Mode of Conception

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>t</th>
<th>P*</th>
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<td>Right eye</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>R1 (mm)</td>
<td>NC</td>
<td>34</td>
<td>7.20</td>
<td>0.29</td>
<td>7.14</td>
<td>8.04</td>
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<td>0.25</td>
<td>7.02</td>
<td>7.52</td>
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<td>R2 (mm)</td>
<td>NC</td>
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<td>6.80</td>
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<td>-2.466</td>
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<td>29</td>
<td>6.63</td>
<td>0.24</td>
<td>6.65</td>
<td>7.18</td>
<td>6.16</td>
<td>-2.466</td>
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<td>SE (D)</td>
<td>NC</td>
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<td>2.6</td>
<td>1.5</td>
<td>3.0</td>
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<td>4.0</td>
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<td>AL (mm)</td>
<td>NC</td>
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<td>0.4</td>
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<td>15.9</td>
<td>17.5</td>
<td>0.311</td>
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<td>16.6</td>
<td>0.5</td>
<td>16.6</td>
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<td>ACD (mm)</td>
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<td>2.3</td>
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<td>2.6</td>
<td>-0.488</td>
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<td>2.3</td>
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<tr>
<td>LT (mm)</td>
<td>NC</td>
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<td>IOP (mm Hg)</td>
<td>NC</td>
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<td>3.0</td>
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<td>18.0</td>
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<tr>
<td>CCT (μm)</td>
<td>NC</td>
<td>34</td>
<td>559.3</td>
<td>40.1</td>
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<td>490.4</td>
<td>630.4</td>
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<tr>
<td></td>
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<td>51.0</td>
<td>569.6</td>
<td>506.0</td>
<td>700.4</td>
<td>0.563</td>
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</table>

Values in bold type are statistically significant. IVF, in vitro fertilization; NC, natural conception; R1 and R2, horizontal and vertical corneal radius of curvature; SE, spherical equivalent; AL, axial length; ACD, anterior chamber depth; LT, lens thickness; IOP, intraocular pressure; CCT, central corneal thickness; Med, median.

*P values were derived from *t*-tests for two independent samples.

### Discussion

Assisted reproduction accounts for up to 4% of births in some countries. These technologies are associated with high rates of multiple birth, prematurity, and low birth weight. Besides the risks inherent to these factors, and in addition to parental selection bias and side effects of the medications used in IVF, the introduction of new procedural techniques that involve intracellular and biological manipulations has raised concerns of increased risk for congenital cardiac, urogenital, upper gastrointestinal, and other chromosomal anomalies.

Ocular findings have also been reported in infants conceived by IVF, including reduced visual acuity, anisometropia, and ocular malformations, in addition to a possible increased risk for retinoblastoma. The authors of a recent Swedish study, which found an increase in anomalies in the eye, head, and neck in infants born by IVF and other reproduction technologies, concluded that ART should be considered potentially teratogenic, thus requiring that information be given to the physicians and the public. A Danish population-based cohort study of 9255 IVF children showed an increased risk for cerebral palsy because of the large proportion of preterm deliveries.

At the same time, however, other studies have demonstrated no difference in neurologic or developmental outcome between infants conceived by IVF or conceived naturally. One prospective study of 21 infants born after in vitro maturation.
length and refractive value was noted, indicating a disturbance resulting from preterm delivery. The results of this oculometric study showed that prematurity (without retinopathy of prematurity) may influence ocular growth. Therefore, in the present study, we examined full-term infants and excluded those with neurologic diseases or malformations. The only difference between the groups was the mode of conception.

We found no statistically significant differences between the naturally conceived and IVF infants in refraction, axial length, lens thickness, anterior chamber depth, and intraocular pressure. Biometric values were similar to those in our previous study. Corneal curvature, however, was less steep in the present study, with the mean corneal radii of curvature in the premature infants (previous study) measuring 6.61 mm (SD = 0.7) at PCA 37 weeks and 6.63 mm (SD = 0.26) at PCA 41 weeks. Given that the cornea flattens with maturation and growth, these differences may be an effect of prematurity on corneal development.

In the present study, the corneal radius of curvature was significantly greater in the IVF infants than in the naturally conceived infants of birth weight less than 3000 g or body length less than 48.5 cm. The differences were not significant for the heavier or longer infants. Interestingly, our study of premature neonates yielded a significant correlation between lower corneal curvature and greater birth weight and between lower corneal curvature and increased PCA. As in premature infants, the steeper cornea in the smaller full-term IVF infants compared with the full-term naturally conceived infants may reflect delayed maturation. This assumption may also hold true for corneal thickness, which was significantly greater in the IVF infants smaller than 48.5 cm than in the natural conception group (Table 2).

A previous study of preterm infants reported a mean central corneal thickness of 691 μm at 31 weeks that decreased to 564 μm at term, concomitant with an increase in corneal diameter. The authors suggested that growth of the eye, with possible remodeling and stretching of the collagen fibers, may play a role in the reduction of central corneal thickness. However, the process of corneal maturation in terms of thickness remains controversial. Some researchers found that the central corneal thickness of full-term infants was greater than that of adults and that it decreased to adult values by age 2 to 4 years. By contrast, a more recent study concluded that after age 6 months, pediatric central and paracentral corneal thickness increases slowly over time and reaches adult value at 5 to 9 years.

The values for central corneal thickness in our series, measured at 36 to 72 hours, with no correlation to gestational age, birth weight, or body length, were lower than the 581 ± 77 μm reported in a Danish series, and the 573 ± 52 μm reported by Portellina and Belfort, who noted higher values at 24 hours of life than after 48 to 72 hours. Accordingly, in the series of 300 newborns of Remon et al. central corneal thickness measured 611 ± 58 μm at 1 day and 585 ± 52 μm subsequently until the age of 6 days. In addition to age, some of the differences in pachymetric values among the studies may be explained by variability in time after birth and by differences in ethnicity.

Our biometric values were similar to those in previous series. The mild hypermetropia noted in both our groups (+2 to +2.6 D) is consistent with that in previous studies. The high rate of a family history of myopia in the infants with myopia in both our groups is noteworthy.

Although there was no statistically significant difference in IOP by mode of conception in the present study, IOP in the whole cohort was lower (Table 2) than that in our previous series of premature neonates (13.2 mm Hg [SD ± 3.6]). Our use of an eye speculum in the present study might have contributed to this difference. Moreover, because central corneal thickness was not measured in the previous study, it is unclear whether the higher IOP in the premature infants reflected differences in pachymetry values.

In conclusion, IVF apparently has no effect on refraction, intraocular pressure, axial length, lens thickness, or retinal vascularization of healthy, full-term infants early in life. The steeper corneal curvature and the greater central corneal thickness in the smaller IVF infants might have reflected delayed corneal maturation. Our results may aid pediatricians and ophthalmologists in assessing ocular dimensions in healthy infants conceived by IVF.

Acknowledgments

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