Glaucoma following cataract surgery in the first two years of life: frequency, risk factors and outcomes from IoLunder2

## Authors:

Ameenat Lola Solebo<sup>1,2,3,4</sup>, Jugnoo S Rahi<sup>1,2,3,4</sup>, on behalf of the British Congenital Cataract Interest Group

- National Institute for Health Research Biomedical Research Centre at UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital, London UK
- 2. Great Ormond Street Hospital for Children NHS Trust, London UK
- 3. National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
- Ulverscroft Vision Research Group, Institute of Child Health, University College London, UK

## Abstract

Background: We investigated glaucoma related adverse events, predictors and impact at five years following surgery in the IoLunder2 cohort

Methods: Population based observational cohort study of children undergoing cataract surgery aged 2 years or under between January 2009 to December 2010. Glaucoma was defined using internationally accepted taxonomies based on the consequences of elevated intraocular pressure. Glaucoma related adverse events were any involving elevated intraocular pressure. Multivariable analysis was undertaken to investigate potential predictors of secondary glaucoma with adjustment for within-child correlation in bilateral cataract. Unilateral and bilateral cataract were analysed separately. Results: Complete follow-up data were available for 235of 254, 93% of the inception cohort. By five years after primary cataract surgery, 20% of children with bilateral cataract and 12% with unilateral had developed secondary glaucoma. Glaucoma related complications had been diagnosed in 24% and 36% of children, respectively. Independent predictors of glaucoma were younger age at surgery (adjusted odds ratio for reduction of week in age:1.1, 95% CI 1.1–1.2, p<0.001); the presence of significant ocular comorbidity (adjOR3.2, 95%CI 1.1–9.6, p=0.01); and shorter axial length (adj OR for each mm 1.7, 95% CI 10.0–1, p=0.05) for bilateral cataract. Shorter axial length was the single independent factor in unilateral disease (adjOR9.6, 95% CI 1.7–52, p=0.009) Conclusions: Both younger age at surgery (the strongest marker of ocular 'immaturity') and smaller ocular size (a marker of both immaturity and developmental vulnerability) can be used to identify

those at greatest risk of glaucoma due to early life cataract surgery.

## Precis

We report findings from IoLunder2 on the relationship between ocular size and age in determining childhood aphakic / pseudophakic glaucoma risk, and present a novel risk algorithm for children undergoing early life surgery.

#### **INTRODUCTION**

Congenital and infantile cataract is an important and preventable cause of childhood blindness throughout the world.<sup>1</sup> Prompt surgical treatment is key to good visual outcomes.<sup>2-4</sup> However, surgery creates a life-long risk of secondary aphakic or pseudophakic glaucoma,<sup>5 6</sup> which has a particularly poor prognosis,<sup>7</sup> and often requires multiple medical and surgical interventions.<sup>7</sup> Indeed the ultimate visual outcome can be poorer than that which occurs in un-operated cataract.<sup>6</sup>

The aetiology of secondary aphakic and pseudophakic glaucoma is poorly understood. Prior to the introduction of modern microsurgical techniques, which allow safer and more thorough removal of the cataract and anterior vitreous, pupil block mechanisms accounted for the majority of cases.<sup>8</sup> <sup>9</sup> Open angle secondary glaucoma, which presents more insidiously, is now the predominant disease type seen after childhood cataract surgery.<sup>10</sup> Age at primary surgery (as a proxy for ocular development) appears to be a critical factor in disease pathogenesis.<sup>2 5 11-14</sup> Other postulated risk factors include ocular size, and the presence of persistent fetal vasculature.<sup>12 14</sup> However, there is still uncertainty with regards to the 'sufficient' and or 'necessary' risk factors for the development of secondary glaucoma following congenital or infantile cataract surgery.

IoLunder2 is a UK and Ireland prospective observational study of outcomes following surgery with and without intraocular lens (IoL) implantation in children aged under or equal to 2 years old. We have previously reported outcomes for children free from significant ocular anomaly, that is those who were eligible, by clinical consensus, for IoL implantation.<sup>15</sup> These included the lack of an association between IoL implantation and the risk of glaucoma.<sup>2</sup> We now present glaucoma related adverse events at five years following surgery for the whole IoLunder2 cohort, interrogating the postulated predictors of secondary glaucoma, and describing the impact of glaucoma on this nationally representative population of children with congenital or infantile cataract.

## MATERIALS AND METHODS

The details of case definition, ascertainment, and data collection for IoLunder2 have been reported in detail.<sup>2 16</sup> Briefly, children aged two years and under undergoing surgery for congenital or infantile cataract, in the UK or Ireland, between 1st January 2009 and 31st December 2010 were eligible for

inclusion. Data on potential predictors of outcome and confounders, agreed a priori by evidence based consensus, were collected prospectively using standardised proforma.

Glaucoma related adverse events comprised ocular hypertension, pupil block and glaucoma. Ocular hypertension was defined as IOP  $\geq$ 21 mm Hg. Transient ocular hypertension was defined as elevated IOP which resolved with cessation of topical steroids. Cases which did not resolve were classified as persistent ocular hypertension. Pupil block was defined as ocular hypertension in the context of a history of obstruction of aqueous flow through the pupil. Glaucoma was defined using the 2001 British Infantile and Childhood Glaucoma ('BIG eye') study group taxonomy: *'the presence of a combination of clinical signs consistent with high intraocular pressure (\geq21mm Hg), such as: optic disc cupping \geq0.3 or disc asymmetry \geq0.2, progressive disc cupping, buphthalmos, enlarged corneal diameter, corneal oedema, Descemet's membrane splits / Haab's striae, visual field defects, or progressive myopia'.<sup>7</sup> This is coterminous with the World Glaucoma Association definition of childhood glaucoma as intraocular pressure (IOP) related damage to the eye, comprising increased cup-to-disc ratio, visual fields changes, ocular enlargement, myopic shift, or Haab striae.<sup>11 17</sup> As well as the incidence, type and date of diagnosis of the glaucoma related adverse event, we collected data on central corneal thickness, and glaucoma management.* 

Age at surgery was analysed as both a continuous and a categorical variable anchored in clinically relevant milestones.<sup>16</sup> Variables assessed as potential risk factors for glaucoma comprised eye laterality (right versus left eye); age at diagnosis or at surgery; axial length and horizontal corneal diameter, both as continuous variables and categorised into severe or simple microphthalmia or microcornea; interocular axial length difference; the presence of persistent fetal vasculature or of significant ocular abnormality; surgeon; surgical technique; primary IoL implantation; bag versus sulcus IoL fixation; viscosity of per operative oculoviscous device; occurrence of per operative iris trauma, per or post-operative complication or subsequent secondary surgery; use of post operative topical or systemic corticosteroid; and family residence socicoenomic status. Further details on the definitions of these variables are provided (appendix 1).

Multivariable logistic and Cox regression was used to model the association between potential predictors and the risk of glaucoma, and time to glaucoma diagnosis. Cases in which IoL implantation

was undertaken, but was reversed perioperatively, were analysed within the IoL group. Children diagnosed with glaucoma related adverse events prior to cataract surgery, and those diagnosed with Oculocerebrorenal syndrome (Lowe, a cataract-glaucoma syndrome)<sup>18</sup> were excluded from the regression analysis. Outcomes following unilateral and bilateral cataract surgery were analysed separately. Data from both eyes of children with bilateral cataract were used with robust variance estimates to account for within-child correlation. Associations are reported with adjustment for known confounding factors.

Prior to regression analysis, correlations between the potential predictors of outcome were investigated using non-parametric tests ( $\chi^2$ , Mann Whitney U, Kruskal-Wallis and Spearman's correlation coefficient) with an alpha error of less than 5% (p<0.05) considered to be supportive of a correlation. Multivariable analysis was undertaken using backward stepwise regression and included those variables significant at p<0.1 level in initial univariable analysis. Where variables were correlated, the more "statistically significant" factor was selected for inclusion in the multivariable analysis. We compared model fit with and without two-way interaction terms. We retained factors in the multivariable model if they altered the odds ratio estimate by more than 10% or were independently associated at a 5% significance level. The results of multivariable analyses were used to stratify proportions of disease frequency and construct relative frequency grids for the diagnosis of glaucoma. Analyses were undertaken using Stata (SE V15.1).

Ethics approval was obtained from the Health Research Authority in the UK, and through institutional committees in Ireland. Written informed consent was obtained from the parents or guardians of all patients.

## RESULTS

254 children were recruited to IoLunder2. Seven of these children died during the 5-year follow-up period, and 12 were lost to follow-up, (4 of whom emigrated). As previously reported,<sup>2</sup> complete 5-year follow-up data were available for 235 (93%) of the original cohort, comprising 106 girls (45%) and 129 boys (55%), and 92 children with unilateral cataract, (39%) and 143 (61%) with bilateral cataract.

## Pre and per-operative characteristics

Baseline sociodemographic and clinical characteristics by bilaterality and by IoL implantation status (aphakia or primary IoL implantation) are described in Table 1. Children living in relative deprivation are over-represented within the IoLunder2 cohort : 61 children (27%) lived in an area within the lowest quintile of Index of Multiple Deprivation score, <sup>19</sup>  $\chi^2$  p<0.05), with a positive univariable association between living in relative deprivation and undergoing surgery without IoL implantation. Almost a third of operated eyes (116/378, 30.7%) had an additional significant ocular abnormality, comprising complex PFV (manifestations other than isolated posterior capsule involvement),<sup>20</sup> other ocular structural anomaly, severe microcornea (horizontal corneal diameter less than 9.5mm), or severe microphthalmos (axial length less than 16mm). 346 of the 378 operated eyes (91.5%) underwent surgery involving a corneo-limbal wound, anterior capsulorhexis, primary posterior capsulorhexis and anterior vitrectomy. 346 of the 378 eyes received local corticosteroids via either intraocular, subconjunctival, subtenon or orbital floor injection upon completion of primary surgery. Intensive post operative topical steroids regimens (drops at least two hourly during the day for the first week) were prescribed following surgery for 40.0% of eyes (151/378).

 Table 1. Sociodemographic and clinical characteristics and peri and post-operative management

 details of subjects

|   | Bilateral cataract   |  |                              | Unilateral cataract           |                               |                         |
|---|--|--|------------------------------|-------------------------------|-------------------------------|-------------------------|
|   | Aphake<br>n=85<br>(170 eyes)                                     | IoL<br>n=58<br>(116 eyes)  | Total<br>n=143<br>(286 eyes) | Aphake<br>n=45                | IoL<br>n=47                   | Total<br>n=92           |
| Demographic details   |  |  |                              |                               |                               |                         |
| Sex (female)  | 41 (48%)   | 25 (43%)   | 66 (46%)                     | 20 (44%)                      | 20 (43%)                      | 40 (43%)                |
| Ethnicity<br>White British / Irish<br><i>Missing</i>                                | 58 (75%)<br>8  | 37 (67%)<br>3  | 95 (72%)**<br>11             | 26 (63%)<br>4                 | 36 (80%)<br>2                 | 62 (72%)**<br>6         |
| Socioeconomic status<br>Living in area of relative<br>deprivation (lowest quintile) | 36 (44%)   | 15 (28%)*  | 51 (38%)**                   | 7 (17%)                       | 3 (7%)                        | 10 (11%)                |
| Missing   | 3  | 5  | 8                            | 3                             | 4                             | 7                       |
| Age at diagnosis in weeks<br>Age at surgery in months                               | $ \begin{array}{c} 1 \\ (0.72) \\ 1.5 \\ (0.3, 17) \end{array} $ | $ \begin{array}{r} 10 \\ (0.97) \\ 4 \\ (0.7, 23)* \end{array} $ | $2 \cdot 4$                  | $1 \\ 0.68 \\ 1.6 \\ (1, 19)$ | 20<br>0-94<br>7<br>(0.5, 23)* | $2 \cdot 2$<br>(0.5.23) |
| Clinical characteristics  | (0.3-17)   | (0.7-2.3)  | (0.3-23)                     | (1-17)                        | (0.3-23)                      | (0.3-23)                |
| Ocular co-morbidity (eyes, %)<br>Microphthalmia or<br>microcornea                   | 118 (69%)  | 68 (59%)   | 186 (65%)                    | 26 (58%)                      | 25 (53%)                      | 51 (55%)                |
| Persistent fetal vasculature  | 14 (8%)  | 8 (7%)   | 22 (8%)                      | 29 (64%)                      | 14 (30%)                      | 43 (47%)                |
| Significant ocular co-<br>morbidity   | 66 (39%)   | 14 (12%)*  | 80 (28%)                     | 27 (60%)                      | 9 (19%)*                      | 36 (39%)                |
| Systemic disorder or neurodevelopmental impairment                                  | 29 (34%)   | 15 (26%)   | 44 (31%)                     | 2 (4%)                        | 6 (13%)                       | 8 (9%)                  |
| Management  |  |  |                              |                               |                               |                         |
| Perioperative management (eyes,<br>%)<br>Corneolimbal wound +                       | 156 (92%)  | 102 (91%)  | 259 (92%)                    | 43 (96%)                      | 44 (94%)                      | 87 (95%)                |
| capsulorhexis + PPC + AV<br>Implantation of hydrophobic<br>acrylic implant          | -  | 114 (98%)  | -                            | -                             | 47 (100%)                     | -                       |
| Periocular or intraocular<br>steroids on completion                                 | 162 (95%)  | 107 (92%)  | 269 (94%)                    | 41 (91%)                      | 45 (96%)                      | 86 (93%)                |
| Intensive regimen of topical steroids post op                                       | 65 (38%)   | 53 (45%)   | 118 (41%)                    | 16 (36%)                      | 17 (36%)                      | 33 (36%)                |
| Post operative visual rehabilitation  |  |  |                              |                               |                               |                         |
| Contact lenses +/- glasses<br>Glasses only  | 21 (25%)<br>60 (72%)   | 5 (9%)<br>48 (86%)   | 26 (18%)<br>108 (78%)        | 11 (24%)<br>17 (38%)          | 1 (2%)<br>42 (89%)            | 12 (13%)<br>59 (60%)    |
| Any occlusion / penalisation<br>therapy   | 15 (18%)   | 22 (39%)   | 37 (26%)                     | 24 (53%)                      | 36 (77%)                      | 60 (65%)                |
| Good overall concordance with occlusion / penalisation                              | 11/15<br>(73%)   | 14/22<br>(64%)   | 25/37<br>(69%)               | 18/24<br>(75%)                | 30/36<br>(83%)                | 48/60<br>(80%)          |

PPC= primary posterior capsulotomy, AVity=anterior vitrectomy

Data are n (children,%) and median(range) unless otherwise stated. All data available for full cohort unless otherwise stated.

Children may have more than one ocular morbidity, perioperative management type, or postop visual rehabilitation type, so totals may>100%,

\*Statistically significant difference aphakia versus IoL.

\*\*Statistically significant difference IoLunder2 cohort versus general national population<sup>21</sup>

## Glaucoma related adverse events

By the end of the fifth post-operative year, 105 of 370 eyes (28.4%) had developed glaucoma, ocular hypertension, or pupil block. 47 eyes (12.8%) of 39 children (16.6%) had secondary glaucoma, and 35 operated eyes had persistent ocular hypertension (table 2). Central corneal thickness (CCT), measured in 13 of these eyes, ranged from 577 - 713 microns, median 629, IQR 610 - 652. CCT was only measured in 9/268 eyes of children without glaucoma.

|                   | Bilateral cataract* |              | Unilateral cataract |  |
|-------------------|---------------------|--------------|---------------------|--|
|                   | 278 eyes            | 138 children | 92 eyes / children  |  |
| No IOP related    | 209                 | 86           | 59                  |  |
| complications     | (75.2%)             | (62%)        | (64.1%)             |  |
| Glaucoma          | 36                  | 28           | 11                  |  |
|                   | (9%)                | (19.6%)      | (12.0%)             |  |
| Persistent ocular | 24                  | 17           | 11                  |  |
| hypertension      | (8.6%)              | (12.2%)      | (12.0%)             |  |
| Transient ocular  | 3                   | 2            | 6                   |  |
| hypertension      | (1.1%)              | (1.4%)       | (6.5%)              |  |
| Pupil block       | 6                   | 5            | 2                   |  |
|                   | (2.2%)              | (3.6%)       | (2.2%)              |  |

Table 2. Frequency of glaucoma related complications at five years following surgery

\* Excludes 2 children with bilateral cataract who had been diagnosed with glaucoma prior to cataract surgery, and 2 children with Lowe syndrome.

In children with bilateral cataract, median time to post operative glaucoma diagnosis was 4.4 months (range 0.4m - 45.3m, and interquartile range (IQR) 1.8m - 23m). For children with unilateral cataract, median time to post operative glaucoma diagnosis 1.5 months (range 0.5m - 8.5m and IQR 0.9m - 2.7m).

### Factors associated with risk of glaucoma

There was strong statistical correlation between the variables identified as potential risk factors for secondary glaucoma (see supplementary table S1). Increasing age at surgery correlated with increasing axial length, and both were associated with the use of primary IoL implantation. Univariable regression analysis identified younger age at surgery, shorter axial length, the co-existence of another significant ocular abnormality, per-operative iris trauma, and leaving the eye aphakic as potential risk factors for the development of glaucoma (see supplementary table S2). From

the multivariable regression logistics and survival models, accounting for with within-child clustering for bilateral cases, the independent predictors of post-operative glaucoma in those with bilateral cataract were younger age at surgery, the presence of a significant ocular abnormality, and smaller axial length (table 3). The independent predictor of glaucoma for children with unilateral cataract, following adjustment for age at surgery, was smaller axial length (table 3). Figure 1 illustrates the variation in rate of development of postoperative glaucoma with variation in age at cataract surgery. Following adjustment for age at surgery and axial length, IoL implantation was not associated with the risk of glaucoma for children with either bilateral or unilateral cataract.

Table 3: Factors independently associated with the risk of post-operative glaucoma

| Bilateral cataract                |   |         |
|-----------------------------------|---|---------|
|                                   | Adjusted odds ratio (OR) (95% CI)                               | р       |
| Decreasing age at surgery (weeks) | 1.12<br>(1.05 - 1.18)   | < 0.001 |
| Significant ocular abnormality    | 3.20<br>(1.06 - 9.63)   | 0.04    |
| Decreasing axial length           | length 1.36<br>(1.01 - 1.90)                                    |         |
|                                   | Adjusted hazard ratio (HR) (95% CI)                             | р       |
| Decreasing age at surgery (weeks) | Exerctasing age at surgery (weeks) $\frac{1.05}{(1.02 - 1.09)}$ |         |
| Significant ocular abnormality    | 2.43<br>(1.13 - 5.20)   | 0.02    |
| Unilateral cataract               |   |         |
|                                   | Adjusted odds ratio (OR) (95% CI)                               | р       |
| Decreasing axial length (mm)*     | gth (mm)* $2.13$<br>(1.08 - 4.17)                               |         |
| Axial length <16mm*               | 9.60<br>(1.73 – 52.22)  | 0.03    |
|                                   | Adjusted odds ratio (OR) (95% CI)                               | р       |
| Axial length <16mm*               | 7.46<br>(1.65 – 34.00)  | 0.009   |

\*Adjusted for age at surgery

#### Figure 1. Nelson-Aalen hazard curves showing the occurrence of post-operative glaucoma by

## age at cataract surgery

(figures available at end of manuscript)

The stratification of risk of glaucoma by presence of significant ocular anomaly (bilateral cataract), age at surgery (unilateral and bilateral cataract) and axial length at surgery (unilateral and bilateral cataract) was used to construct a relative risk grid for diagnosis of secondary glaucoma within the five years following primary surgery (figure 2).

**Figure 2. Relative risk grids for diagnosis of secondary glaucoma by fifth post-operative year** \*or children with other significant ocular abnormality: HCD<9.5mm, complex persistent fetal vasculature, or other structural anomaly

## Outcomes for children with secondary glaucoma

25 eyes of 23 children with bilateral cataract underwent interventional procedures for glaucoma. Initial procedures comprised cyclodiode laser (n=12 eyes, of which 2 proceeded to drainage tube surgery, and 2 to goniotomy), tube drainage surgery (n=7, of which 4 proceeded to cyclodiode laser), and goniotomy (n=6, of which 4 progressed to tube surgery, 1 to cyclodiode, and 1 to both cyclodiode and tube surgery). The median number of procedures was 2.6 per child (ranging from 0 – 6). Following glaucoma tube surgery, 2 children developed endophthalmitis. No child within IoLunder2 developed endophthalmitis following primary cataract surgery.<sup>2</sup> Amongst children with bilateral cataract surgery who developed glaucoma, median final uniocular acuity was 0.74 logMAR (range 0.05 - 3, IQR 0.62 – 1.2), compared to 0.4 logMAR (range 0 - 3, IQR 0.3 – 0.9) for those eyes of children without glaucoma. For the subgroup of those who had undergone glaucoma surgery, median acuity was 0.9 logMAR (range 0.2 - 3, IQR 0.7 – 2.4).

Nine children with unilateral cataract underwent glaucoma procedures. Initial procedures comprised cyclodiode laser (n=3 eyes, of which 2 underwent subsequent tube drainage surgery), tube drainage surgery (n=2), and goniotomy (n=4, of which 1 underwent subsequent cyclodiode laser). The median number of procedures was 1.4 per eye (ranged from 0 - 3). Median acuity of eyes diagnosed with

glaucoma was 1.4 logMAR (range 0.3 - 3, IQR 0.56 - 2.4), and 2.4 (range 0.375 - 3, IQR 1.5 - 2.7) for those eyes which underwent glaucoma surgery. By comparison, median acuity for eyes which did not have glaucoma was 0.9 (range 0 - 3, IQR 0.38 - 1.5).

#### CONCLUSIONS

In a national cohort of children undergoing cataract surgery in the first two years of life, 20% of children with bilateral cataract and 12% of children with unilateral cataract had developed secondary glaucoma by five years after primary surgery. An additional 24% and 36% of children with bilateral and unilateral cataract respectively, had developed a glaucoma related outcome. Incident cases were noted four years following surgery, underscoring the on-going risk. The factors most strongly associated with the risk of developing glaucoma were age at surgery, and ocular size (axial length) and the presence of ocular structural anomalies. No child who underwent cataract surgery aged older than 7 months developed glaucoma. The development of glaucoma was associated with significant visual morbidity, and multiple subsequent re-operations.

This prospective study of outcomes following cataract surgery amongst a nationally representative<sup>22</sup> inception cohort of children aged under 2 years at the time of surgery used systematic, standardised data collection through a national clinical network, the British Isles Congenital Cataract Interest Group. This collaborative clinical network also agreed, a priori by evidence based consensus, on definitions and classifications of glaucoma and potential predictors of outcome, minimising the potential for misclassification. Clinicians were asked to classify glaucoma as open or closed angle type. Aphakic and pseudophakic glaucoma, in the absence of pupil block, has been assumed to be due to an open angle mechanism, with investigators describing an abnormal, amorphous appearance to the trabecular meshwork.<sup>69 12 23</sup> However, the IoLunder2 data collection instruments did not request details of gonioscopic examination or other direct visualisation of the angle, which in most children aged under 5 years would require contact methods of examination, usually as an examination under general anaesthetic. We have assumed that reporting clinicians have correctly classified disease. Future studies of secondary glaucoma should take advantage of the emerging imaging technologies which allow non-contact high resolution imaging of angle morphology.<sup>24</sup>

Increased central corneal thickness has been reported following early childhood cataract surgery, possibly due to iatrogenic arrest of normal developmental processes due to either per-operative microtrauma or release of lens proteins.<sup>25</sup> This leads to over diagnosis of ocular hypertension. To limit the impact of this potential misclassification, IoLunder2 employed the internationally accepted definition of disease based on the pathological consequences of high IOP rather than IOP per se. Secondary glaucoma is now the most common sight threatening post-operative outcome of childhood cataract surgery, accounting for a third of all secondary childhood glaucoma in industrialised countries such as the United Kingdom.<sup>7</sup> Variation in definitions used in prior research make it difficult to directly understand trends and risk factors.<sup>5711-14</sup> The extant literature on secondary glaucoma after cataract surgery suggest that between 10% and 25% of aphakic eyes will develop glaucoma by the 10th year following congenital or infantile cataract surgery.<sup>5 11-13 26</sup> This is consistent with our findings. Equally, our findings on timing of glaucoma onset coincide with population based and large scale longitudinal studies of outcomes following congenital and infantile cataract surgery, which consistently show that the frequency of glaucoma increases with the duration of follow up, with approximately 5% of operated eyes developing secondary glaucoma each year.<sup>5 12 27</sup> Notably, glaucoma continued to be diagnosed years following surgery in children with bilateral disease in IoLunder2. However, in the smaller subgroup of children with unilateral cataract, secondary glaucoma was diagnosed in the first year following surgery. This is not consistent with other studies, <sup>5 11 12</sup> and may be a chance finding. The planned longer term follow up of the IoLunder2 cohort will prove useful in investigating potential differences in pathogenic processes for children with unilateral or bilateral cataract.

Age at surgery was a key risk factor for the development of secondary glaucoma in IoLunder2, consistent with other reports.<sup>5 12 14</sup> There was previously uncertainty regarding the role of ocular size in predicting glaucoma, due to prior studies either failing to report ocular size,<sup>14</sup> or comprising small study populations with limited power to detect statistically significant clinical associations.<sup>27</sup> Our findings suggest that both age at surgery and ocular size, as markers of developmental vulnerability, should be used independently to predict the risk of glaucoma due to early life cataract surgery. Persistent fetal vasculature (PFV) has not consistently been found to be a significant risk factor,<sup>26 28</sup>

but in prior research the phenotypology of PFV is so variable that the case mix (selection bias) may be responsible for the absence of prior robust reported associations.<sup>20 29</sup> IoLunder2 suggests that the presence of 'complex' PFV (ie significant structural disturbance beyond the presence of a posterior capsule remnants) is a risk factor for the development of post-operative glaucoma.

Glaucoma was only diagnosed in children who underwent surgery during the first 6 months of life. This may have been due to chance, but a "threshold" effect of age cannot be ruled out. Others have investigated this possibility using an ad hoc cut off of 9 months of age, reporting an increased risk of glaucoma (n=322 children, adjusted hazard ratio =7.0 [CI 3/6 - 13.7]<sup>13</sup> and n=234 children, adj HR=2.9 [CI 1.3 - 7.7])<sup>26</sup>. Should a threshold exist, it is likely to comprise an age band occurring ater than the accepted critical sensitive period for visual development.<sup>30</sup> Consequently, there is unlikely to be a simple answer to the question of how to balance the risk of amblyopia with the risk of glaucoma when planning timing of congenital cataract surgery.

Higher proportions of children were diagnosed with glaucoma in the first post-operative year than were reported by an earlier UK cohort study.<sup>5</sup> Paradoxically, this may be due to the younger age at surgery in the IoLunder2 cohort, achieved through greater focus on early intervention in order to improve visual outcomes.<sup>3</sup> Newborn and infant examination of the red reflex are now rightly mandated in the UK and similar health settings. We suggest that the focus of research in congenital cataract should be on other obstacles to good outcome, particularly averting glaucoma. Greater understanding of the mechanism by which the insult of cataract surgery causes glaucoma in vulnerable eyes is urgently needed. This will require premorbid data on the angle through high definition ocular imaging. Normative gonioscopic data on the development of the anterior segment, specifically the differentiation of the angle in the first few years of life, will be difficult to obtain and would require examination under anaesthetic or sedation, but would be of great value. This could be complemented by the use of hand-held, non-contact optical coherence tomography (OCT) instruments enabling imaging of Schlemm's canal, trabecular meshwork and angle morphology.<sup>24</sup> Genomic investigation, and identification of molecular biomarkers of glaucoma risk will further enable personalised management of children following early life cataract surgery.

We anticipate further incident cases of secondary glaucoma within IoLunder.<sup>5</sup> Longer term follow up of this cohort, and investigation of anatomical differences between those free of glaucoma, those with ocular hypertension, and with early versus late onset glaucoma, should enable greater understanding of this iatrogenic, blinding disorder.

## References

 Solebo AL, Teoh L, Rahi J. Epidemiology of blindness in children. Archives of disease in childhood 2017;102(9):853-57. doi: 10.1136/archdischild-2016-310532 [published Online First: 2017/05/04]

2. Solebo AL, Cumberland P, Rahi JS. 5-year outcomes after primary intraocular lens implantation in children aged 2 years or younger with congenital or infantile cataract: findings from the IoLunder2 prospective inception cohort study. The Lancet Child & adolescent health 2018;2(12):863-71. doi: 10.1016/s2352-4642(18)30317-1 [published Online First: 2018/11/06]

3. Chak M, Wade A, Rahi JS. Long-term visual acuity and its predictors after surgery for congenital cataract: findings of the British congenital cataract study. Invest Ophthalmol Vis Sci 2006;47(10):4262-69.

4. Birch EE, Cheng C, Stager DR, Jr., et al. The critical period for surgical treatment of dense congenital bilateral cataracts. J AAPOS 2009;13(1):67-71.

Chak M, Rahi JS. Incidence of and factors associated with glaucoma after surgery for congenital cataract: findings from the British Congenital Cataract Study. Ophthalmology 2008;115(6):1013-18.
 Egbert JE, Christiansen SP, Wright MM, et al. The natural history of glaucoma and ocular hypertension after pediatric cataract surgery. J AAPOS 2006;10(1):54-57.

7. Papadopoulos M, Cable N, Rahi J, et al. The British Infantile and Childhood Glaucoma (BIG) Eye Study. Invest Ophthalmol Vis Sci 2007;48(9):4100-06.

8. Simon JW, Mehta N, Simmons ST, et al. Glaucoma after pediatric lensectomy/vitrectomy.
 Ophthalmology 1991;98(5):670-74.

9. Walton DS. Pediatric aphakic glaucoma: a study of 65 patients. Trans Am Ophthalmol Soc 1995;93:403-13.

10. Balekudaru S, Agarkar S, Guha S, et al. Prospective analysis of the predictors of glaucoma
following surgery for congenital and infantile cataract. Eye (Lond) 2018 doi: 10.1038/s41433-0180316-8 [published Online First: 2018/12/19]

 Freedman SF, Lynn MJ, Beck AD, et al. Glaucoma-Related Adverse Events in the First 5 Years After Unilateral Cataract Removal in the Infant Aphakia Treatment Study. JAMA Ophthalmol 2015;133(8):907-14. doi: 10.1001/jamaophthalmol.2015.1329 [published Online First: 2015/05/23]

12. Haargaard B, Ritz C, Oudin A, et al. Risk of glaucoma after pediatric cataract surgery. Invest Ophthalmol Vis Sci 2008;49(5):1791-96.

 Rabiah PK. Frequency and predictors of glaucoma after pediatric cataract surgery. Am J Ophthalmol 2004;137(1):30-37.

14. Mataftsi A, Haidich AB, Kokkali S, et al. Postoperative glaucoma following infantile cataract surgery: an individual patient data meta-analysis. JAMA Ophthalmol 2014;132(9):1059-67. doi: 10.1001/jamaophthalmol.2014.1042 [published Online First: 2014/06/13]

15. Solebo AL, Russell-Eggitt I, Nischal KK, et al. Cataract surgery and primary intraocular lens implantation in children < or = 2 years old in the UK and Ireland: finding of national surveys. Br J Ophthalmol 2009;93(11):1495-98.

16. Solebo AL, Russell-Eggitt I, Cumberland PM, et al. Risks and outcomes associated with primary intraocular lens implantation in children under 2 years of age: the IoLunder2 cohort study. Br J Ophthalmol 2015:bjophthalmol-306394.

17. Weinreb RN, Grajewski A, Papadopoulos M, et al. Childhood Glaucoma. World Glaucoma Association Consensus Series2013.

18. Walton DS, Katsavounidou G, Lowe CU. Glaucoma with the oculocerebrorenal syndrome of Lowe. J Glaucoma 2005;14(3):181-85.

19. Statistics OfN. UK Indices of Multiple Deprivation, 2010.

20. Goldberg MF. Persistent fetal vasculature (PFV): an integrated interpretation of signs and symptoms associated with persistent hyperplastic primary vitreous (PHPV). LIV Edward Jackson Memorial Lecture. American Journal of Ophthalmology 1997;124(5):587.

21. Statistics OoN. ONS: Characteristics of Birth, 2009.

Solebo AL, Russell-Eggitt I, Rahi JS. Accuracy of routine data on paediatric cataract in the UK compared to active surveillance: lessons from the IOLu2 study. Br J Ophthalmol 2013;97(6):757-59.
 Egbert JE, Wright MM, Dahlhauser KF, et al. A prospective study of ocular hypertension and glaucoma after pediatric cataract surgery. Ophthalmology 1995;102(7):1098-101.

24. Daniel MC, Dubis AM, Quartilho A, et al. Dynamic Changes in Schlemm Canal and Iridocorneal Angle Morphology During Accommodation in Children With Healthy Eyes: A Cross-Sectional Cohort Study. Invest Ophthalmol Vis Sci 2018;59(8):3497-502. doi: 10.1167/iovs.17-23189 [published Online First: 2018/07/20]

25. Morrison DG, Lynn MJ, Freedman SF, et al. Corneal Changes in Children after Unilateral
Cataract Surgery in the Infant Aphakia Treatment Study. Ophthalmology 2015;122(11):2186-92. doi:
10.1016/j.ophtha.2015.07.011 [published Online First: 2015/08/15]

26. Swamy BN, Billson F, Martin F, et al. Secondary glaucoma after paediatric cataract surgery. Br J Ophthalmol 2007;91(12):1627-30.

27. Magnusson G, Abrahamsson M, Sjostrand J. Glaucoma following congenital cataract surgery: an 18-year longitudinal follow-up. Acta Ophthalmol Scand 2000;78(1):65-70.

28. Watts P, Abdolell M, Levin AV. Complications in infants undergoing surgery for congenital cataract in the first 12 weeks of life: is early surgery better? J AAPOS 2003;7(2):81-85.

29. Solebo AL, Russell-Eggitt I, Cumberland P, et al. Congenital cataract associated with persistent fetal vasculature: findings from IoLunder2. Eye (Lond) 2016;30(9):1204-9. doi:

10.1038/eye.2016.159 [published Online First: 2016/07/30]

30. Birch EE, Wang J, Felius J, et al. Fixation control and eye alignment in children treated for dense congenital or developmental cataracts. J AAPOS 2012;16(2):156-60.

## A. Bilateral cataract eyes



B. Unilateral cataract



# A. Child with bilateral cataract



## B. Unilateral cataract

Axial length at surgery (mm)

