Association of Weight Gain Acceleration With Risk of Retinopathy of Prematurity

Sila Bal, MD, MPH,¹ Gui-shuang Ying, PhD,² Lauren Tomlinson, BS,¹ and Gil Binenbaum, MD, MSCE, for the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group

¹Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
²Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

Corresponding author.

Article Information

Group Information: Members of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group appear at the end of the article.

Accepted for Publication: July 14, 2019.

Corresponding Author: Gil Binenbaum, MD, MSCE, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, 9-MAIN, Philadelphia, PA 19104 (binenbaum@email.chop.edu).

Published Online: September 5, 2019. doi:10.1001/jamaophthalmol.2019.3447

Author Contributions: Dr Binenbaum had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bal, Binenbaum.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bal, Tomlinson.

Critical revision of the manuscript for important intellectual content: Bal, Ying, Binenbaum.

Statistical analysis: Ying.

Obtained funding: Ying, Binenbaum.

Administrative, technical, or material support: Bal, Tomlinson.

Study supervision: Ying, Binenbaum.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grant 1R01EY021137-01A1 from the National Institutes of Health and the Richard Shafritz Endowed Chair in Pediatric Ophthalmology Research of the Children’s Hospital of Philadelphia.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
Group Information: Members of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study Group include the following: Office of Study Chair: Children's Hospital of Philadelphia, Philadelphia, Pennsylvania: Gil Binenbaum, MD, MSCE (principal investigator [PI]); Lauren A. Tomlinson, BS; and Trang B. Duros, BBA; Data Coordinating Center: University of Pennsylvania Perelman School of Medicine, Philadelphia: Gui-shuang Ying, PhD (PI); Maureen G. Maguire, PhD; Mary Brightwell-Arnold, BA, SCP; James Shaffer, MS; Maria Blanco, BS; Trina Brown, BS; and Christopher P. Helker, MSPH; Clinical Centers: Albany Medical College, Albany, New York: Gerard P. Barry, MD (PI); Marilyn Fisher, MD, MS; Maria V. Battaglia, BS, MS; and Alex M. Drach, BA; Johns Hopkins University, Baltimore, Maryland: Pamela Donohue, ScD (PI); Michael X. Repka, MD; Megan Doherty, NNP; and Jennifer A. Shepard, CRNP; State University of New York at Buffalo; and Women & Children's Hospital of Buffalo, Buffalo, New York: James D. Reynolds, MD (PI); and Erin Connelly; Medical University of South Carolina, Charleston: Edward Cheeseman, MD, MBA (PI); Carol Bradham, COA, CCRC; Allison McAlpine, MD; Sudeep Sunthankar, MD; and Kinsey Shirer, RN; University of Illinois at Chicago: Javaneh Abbassian, MD (PI); and Janet Lim, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Good Samaritan Hospital, Cincinnati, Ohio; and University of Cincinnati, Cincinnati, Ohio: Michael Yang, MD (PI); Elizabeth L. Alfano; and Patricia Cobb, MS; Nationwide Children's Hospital, Columbus, Ohio: David Rogers, MD (PI); Rae R. Fellows, MEd, CCRC; Kaitlyn Loh; Madeline A. McGregor; Thabit Mustafa; Rachel E. Reem, MD; Tess Russell; Rebecca Statttler; and Sara Oravecz; Kapi'olani Medical Center for Women and Children, Honolulu, Hawaii: David Young, MD (PI); Andrea Siu, MPH, RAC; and Michele Kanemori, MD; Indiana University, Indianapolis; and Riley Hospital for Children at Indiana University Health, Indianapolis: Jingyun Wang, PhD (PI); Kathryn Haider, MD; and Elizabeth Hynes, RNC-NIC; University of Iowa Stead Family Children's Hospital, Iowa City: Edward F. Bell, MD (PI); Alina V. Dumitrescu, MD; Jonathan M. Klein, MD; Avanthi S. Ajarapu; Gretchen A. Cress, RN, MPH; Bethany M. Funk; Claire L. Johnson; and Angela C. Platt; Loma Linda University, Loma Linda, California; and Loma Linda University Children's Hospital, Loma Linda, California: Leila Khazaeni, MD (PI); Jennifer Dunbar, MD; Kelley Hawkins; Sharon Lee, RN; and Lily Sung, MD; University of Louisville, Louisville, Kentucky; and Norton Children's Hospital, Louisville, Kentucky: Rahul Bhola, MD (PI); Michelle Bottruff, COA; Neviana Dimova, MD, MS; Rachel Keith, PhD, MSN, NP-C; and Laura Thomas, RN, BSN, CCRN; University of Minnesota, Minneapolis; and University of Minnesota Masonic Children's Hospital, Minneapolis: Jill Anderson, MD (PI); Jordan Gross; Ann Marie Holleschau, CCRP; and Andrea Kramer; Vanderbilt Eye Institute, Nashville, Tennessee; Vanderbilt University Medical Center, Nashville, Tennessee; and Monroe Carell Jr. Children's Hospital at Vanderbilt, Vanderbilt University, Nashville Tennessee: David Morrison, MD (PI); Sean Donahue, MD, PhD; Neva Fukuda, CO; Sandy Owings, COA, CCRP; and Scott Ruark, OD; University of Oklahoma, Oklahoma City; and Children's Hospital at Oklahoma University Medical Center, Oklahoma City: R. Michael Siatkowski, MD (PI); Faizah Bhatti, MD; Vanessa Bergman, COT, CCRC; Karen Corff, APRN, NNP; Kari Harkey, RNC-NIC; Amy Manfredo, APRN-CNP; Shrenik Talsania, MBBS, MPH, CPH; and Terri Whisenhunt, MS, RN; Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and Hospital of the University of Pennsylvania, Philadelphia: Gil Binenbaum, MD, MSCE (PI); Haresh Kirpalani, MD, MSc; Graham E. Quinn, MD, MSCE; Lindsay Dawson, MD; and Lauren A. Tomlinson, BS; Rhode Island Hospital, Providence; and Women and Infants Hospital of Rhode Island, Providence: Wendy S. Chen, MD, PhD (PI); and Deidrya Jackson, MD, MPH; Saint Louis University, St Louis, Missouri; and SSM Health Cardinal Glennon Children's Hospital, St Louis, Missouri: Bradley Davitt, MD (PI); Dawn Goveau, COT; Linda Breuer, LPN; and September Noonan, RN; University of Utah, Salt Lake City; and University of Utah Hospital, Salt Lake City: Robert Hoffman, MD (PI); Joanna Beachy, MD, PhD; Deborah Harrison, MS; Ashlie Bernhise; Bonnie Carlstrom; and Katie Jo Farnsworth, CRC; University of California, San Francisco; UCSF Benioff Children's Hospital, San Francisco, California; and Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California: Alejandro G. de Alba Campanones, MD, MPH (PI); Jacqueline Kemmer, BA; Alexandra Neiman, BA; and Sarah Sitati-Ng'Anda, MD; Seattle Children's, Seattle, Washington; and University of Washington, Seattle: Francine Baran, MD (PI); Kristina Tarczy-Hornoch, MD, DPhil (PI); and Lauren Eaton, MS; The Hospital for Sick Children, Toronto, Ontario, Canada: Nasrin Najm-Tehrani, MD, MSc (PI); Maram Issac, MBBS, MHA; and Robin Knighton; Los Angeles Biomedical Research Institute, Torrance, California; and Harbor-UCLA Medical Center, Torrance, California: Monica Rally Khitri, MD (PI); and Madeline Del
Signore, RN; Crozer-Chester Medical Center, Upland, Pennsylvania: Cynthia Dembofsky, MD (PI); Andrew Meyer, MD (PI); Karen Flaherty; Tracey Harris; and Jamie Heeneke; and Nemours/Alfred I. duPont Hospital for Children, Wilmington, Delaware: Christopher M. Fecarotta, MD (PI); Dorothy Hendricks, MD (PI); Alicia Olivant Fisher, MS; and Mark Paullin, MS; Cost-effectiveness Component: Beth Israel Deaconess Medical Center, Boston, Massachusetts: John Zupancic, MD, MS, ScD (PI); Executive/Editorial Committee: Alejandra de Alba Campomanes, MD, MPH; Edward F. Bell, MD; Gil Binenbaum, MD, MSCE; Pamela Donohue, ScD; David Morrison, MD; Graham E. Quinn, MD, MSCE; Michael X. Repka, MD; David L. Rogers, MD, Lauren A. Tomlinson, BS; Michael Yang, MD; and Gui-shuang Ying, PhD.

Meeting Presentation: This paper was previously presented in part at the Annual Meeting of the Eastern Society for Pediatric Research; March 25, 2017; Philadelphia, Pennsylvania; and at the Annual Meeting of the Association for Research in Vision and Ophthalmology; May 11, 2017; Baltimore, Maryland.

Received 2019 Feb 6; Accepted 2019 Jul 14.

Copyright 2019 American Medical Association. All Rights Reserved.

Key Points

Question

Is fast weight gain acceleration, a surrogate for change in serum insulinlike growth factor 1 level, associated with a higher risk of severe retinopathy of prematurity (ROP)?

Findings

In this secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity study including 6835 infants undergoing ROP examinations at 29 North American hospitals, except in infants with the slowest early postnatal weight gain, increasing late weight gain acceleration was associated with increasing risk of severe ROP up to a threshold, beyond which risk fell.

Meaning

Although early slow weight gain is associated with an increased risk of ROP, the association appears more complex than previously thought, since the timing and rate of weight gain acceleration may also affect the risk of severe ROP.

Abstract

Importance

Early slow postnatal weight gain, a surrogate for low insulinlike growth factor 1 (IGF-1) levels, is predictive of retinopathy of prematurity (ROP). While low IGF-1 levels inhibit retinal vessel growth, a later rise theoretically activates vascular endothelial growth factor, causing neovascularization. Rate of rise of IGF-1 level is represented by weight gain acceleration (WGA) and may be used to evaluate risk of ROP.

Objective

To evaluate whether faster WGA during a later postnatal period is associated with a higher, rather than lower, risk of severe ROP.

Design, Setting, and Participants

This secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) study
included 6835 infants undergoing ROP examinations from 29 hospitals in North America from January 2006 to June 2012. Data were analyzed from September to December 2016.

Main Outcomes and Measures

Early weight gain rate (WGR) during 29 to 33 weeks’ postmenstrual age and late WGA during 34 to 38 weeks’ postmenstrual age were determined using linear regression of daily weight measurements and changes in daily weight measurements, respectively. The primary outcome was the association of late WGA with severe ROP.

Results

Of the 6835 included infants, the mean (SD) birth weight was 1086 (357) g, and the mean (SD) gestational age was 27.9 (2.5) weeks. Risk of severe ROP increased with increasing late WGA up to about the 80th percentile of WGA. After adjusting for birth weight and gestational age, among infants in the lowest early WGR tertile, there was no association of late WGA with severe ROP, and among infants in the moderate and highest early WGR tertiles, the moderate WGA tertiles had the highest risk of ROP (moderate early WGR tertile: adjusted odds ratio, 1.38; 95% CI, 0.98-1.94; highest early WGR tertile: adjusted odds ratio, 1.63; 95% CI, 1.02-2.60).

Conclusions and Relevance

Although much attention has been paid to the association of slow weight gain with ROP, the association may be more complex than appreciated. These findings suggest that low early WGR is associated with severe ROP regardless of subsequent WGA, but if early WGR is moderate or high, subsequent rapid rises in WGR are associated with increasing risk of severe ROP. If validated in additional cohorts, this finding may affect potential therapies, such as the timing of IGF-1 supplementation.

Introduction

Current retinopathy of prematurity (ROP) screening criteria, using birth weight (BW) and gestational age (GA), have high sensitivity but low specificity for identification of infants developing severe ROP.\[^{1,2,3}\]

Identification of slow postnatal weight gain, a proposed surrogate for low insulinlike growth factor 1 (IGF-1) levels, improves specificity of these criteria.\[^{6,7,8,9,10,11}\]

Insulinlike growth factor 1 plays a permissive role in vascular endothelial growth factor (VEGF) activity.\[^{6}\]

In developing retina, increasing metabolic demands and relative hypoxia cause increased VEGF production. However, premature infants have low serum IGF-1 levels owing to loss of maternal sources, inhibiting retinal vessel growth. Eventually, endogenous serum IGF-1 levels increase with increasing infant age and weight, activating VEGF and causing pathologic neovascularization.\[^{6,7,8,9}\]

Low IGF-1 levels have been shown to predict the later development of severe ROP, and IGF-1 supplementation is being investigated.\[^{12}\]

Low early IGF-1 levels and the surrogate measure, slow early postnatal weight gain, are associated with subsequent ROP. However, when considering the aforementioned model of ROP pathogenesis, IGF-1 levels that later rise too quickly may also be deleterious. In the ROP models developed to date, the static value of serum IGF-1 level is represented by change in weight gain, or weight gain rate (WGR). Therefore, a change in serum IGF-1 level would be represented by a change in WGR, or weight gain acceleration (WGA). We sought to determine the association of late postnatal WGA with severe ROP to evaluate the a priori hypothesis that faster WGA later in postnatal life is associated with a higher, rather than lower, risk of severe ROP.
Methods

We conducted a secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) study, a National Institutes of Health–supported, multicenter retrospective cohort study of infants undergoing ROP screening across 29 North American hospitals between January 1, 2006, and June 30, 2012. Infants had known BW, GA, and ROP outcomes and sufficient postnatal daily weight measurements. Examinations were completed by fellowship-trained pediatric ophthalmologists or retinal specialists with ROP expertise. Institutional review board approval was obtained at the Children’s Hospital of Philadelphia and at all hospitals. Informed consent was waived based on the Common Rule.

Statistical Analysis

Based on published work examining timing of changes in IGF-1 level and associations with ROP, periods were established a priori: an early WGR period at 29 to 33 weeks’ postmenstrual age (PMA) and a later WGA period at 34 to 38 weeks’ PMA. Linear regression of daily weight measurements was used to calculate WGR during the early period and changes in daily WGR for WGA during the late period. Weights from the first week of life were excluded owing to the weight loss that occurs in most neonates.

The primary outcome was the association of late WGA with severe ROP, defined as Early Treatment of ROP Study type 1 or 2 ROP in either eye. To explore this association, infants were grouped into centiles by their late WGA; rate of severe ROP was calculated for each centile, and a locally weighted scatterplot smoothing line was used to visualize the association of severe ROP rate with rank of late WGA. In addition, infants were grouped by late WGA into 3 similarly sized groups, and logistic regression assessed the association of late WGA with severe ROP. Potential confounders were controlled for by considering 3 primary, well-established ROP risk factors: BW, GA, and early WGR. In the slowest early WGR tertile, there was no association of late WGA with severe ROP (Figure 2; Table). In the middle early WGR tertile, infants in the middle tertile of late WGA (−0.25 to 0.55 g/d/d) had the highest risk of ROP compared with infants in the lowest late WGA tertile (adjusted odds ratio, 1.38; 95% CI, 0.98-1.94). Similarly, in the highest early WGR tertile, infants in the middle tertile of late WGA had the highest risk of ROP compared with infants in the lowest late WGA tertile (adjusted odds ratio, 1.63; 95% CI, 1.02-2.60).

Discussion

Despite considerable evidence of the association of early slow weight gain with subsequent severe ROP, the association of weight gain with ROP appears more complex than previously appreciated. We found that increasing late WGA during 34 to 38 weeks’ PMA is associated with increasing risk of severe ROP.
severe ROP. However, the effect of late WGA depends on WGR earlier in postnatal development. Low early WGR during 29 to 33 weeks’ PMA was associated with severe ROP regardless of subsequent late WGA. Infants with moderate or high early WGR with subsequent rapid increases in WGR were at increased risk of severe ROP, except for those with the highest late WGA, who had a risk similar to those in the lowest late WGA group, as infants with the highest WGA had higher BW and GA and were generally at lower risk of ROP (eTable in the Supplement).

Our results support the known association of slow early WGR with subsequent ROP. Infants with the lowest early WGR were at high risk of severe ROP, regardless of later WGA, suggesting the effect of slow early WGR overpowers any effect from later WGA, theoretically because it creates a larger imbalance between vascular development and retinal metabolic demand and higher retinal VEGF production. However, infants with moderate or higher early WGR demonstrated a positive association of faster WGA with severe ROP. High late WGA was used as a surrogate for a rapid increase in serum IGF-1 levels. Presumably, in infants with moderate or high early WGR, rapid increases in serum IGF-1 levels result in more robust activation of VEGF and neovascular ROP.

Strengths and Limitations

A strength of our study was the statistical power to examine these associations owing to the large, multicenter cohort. However, there are limitations to consider. We used weight gain as a surrogate for IGF-1 levels, which is more practical than IGF-1 blood testing but may not perfectly correlate with IGF-1 level. Although we controlled for the strongest known ROP risk factors, there may be unaccounted additional known or unknown confounders that may affect weight gain–related ROP risk.

Conclusions

Very slow early WGR is associated with severe ROP. However, higher early WGR followed by subsequent rapid late WGA may also be associated with increased risk of severe ROP, except for in the fastest growing infants. Therefore, effects of exogenous IGF-1 supplementation or other interventions may vary depending on their timing and rate of administration. Though further study of these exploratory study findings is necessary, improved understanding of the complexity of the associations of weight gain with ROP risk may help to further improve ROP prediction.

Notes

Supplement.

eTable. Mean birth weight (BW) and gestational age (GA) of 6835 infants stratified by early weight gain rate (WGR) during 29 to 33 weeks’ postmenstrual age and weight gain acceleration (WGA) during 34 to 38 weeks’ postmenstrual age.

References


**Figures and Tables**
Figure 1.

Association of Late Weight Gain Acceleration With Risk of Severe Retinopathy of Prematurity (ROP) Among 6835 At-Risk Infants

A locally weighted scatterplot smoothing (LOESS) line is used to visualize the association. PMA indicates postmenstrual age.
Association of Late Weight Gain Acceleration With Risk of Severe Retinopathy of Prematurity (ROP) Among 6835 At-Risk Infants by Early Weight Gain Rate During 29 to 33 Weeks’ Postmenstrual Age

A locally weighted scatterplot smoothing (LOESS) line is used to visualize the associations within each tertile. A total of 426 infants (19.0%) in the lowest weight gain rate tertile (<19 g/d), 286 (12.4%) in the middle weight gain rate tertile (19 to 26 g/d), and 156 (6.8%) in the highest weight gain rate tertile (>26 g/d) had severe ROP. PMA indicates postmenstrual age.
### Table.

**Stratified Analysis of the Association of Weight Gain Rate With Weight Gain Acceleration**

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Total, No.</th>
<th>Infants With Severe ROP, No. (%)</th>
<th>Weight Gain Acceleration During 34 to 38 wk Postmenstrual Age, g/d/d</th>
<th>Infants With Severe ROP, No. (%)</th>
<th>Adjusted OR With Severe ROP (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;19 g/d)</td>
<td>2244</td>
<td>426 (19.0)</td>
<td>≤−0.25</td>
<td>119 (17.7)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.25 to 0.55</td>
<td>171 (19.8)</td>
<td>1.06 (0.78 to 1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;0.55</td>
<td>136 (19.2)</td>
<td>1.05 (0.77 to 1.45)</td>
</tr>
<tr>
<td>Middle (19-26 g/d)</td>
<td>2307</td>
<td>286 (12.4)</td>
<td>≤−0.25</td>
<td>77 (9.4)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.25 to 0.55</td>
<td>124 (16.2)</td>
<td>1.38 (0.98 to 1.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;0.55</td>
<td>85 (11.8)</td>
<td>1.11 (0.77 to 1.60)</td>
</tr>
<tr>
<td>High (&gt;26 g/d)</td>
<td>2284</td>
<td>156 (6.8)</td>
<td>≤−0.25</td>
<td>41 (5.1)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.25 to 0.55</td>
<td>63 (9.4)</td>
<td>1.63 (1.02 to 2.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;0.55</td>
<td>52 (6.4)</td>
<td>1.15 (0.71 to 1.86)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; ROP, retinopathy of prematurity.

<sup>a</sup>Adjusted by birth weight and gestational age.