Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants

Luisa Schonhaut, MD, MPH, MSc, Iván Armijo, BSc, Marcela Pérez, MD

OBJECTIVES: The objective of this study was to evaluate the association between gestational age (GA) at birth and risk of developmental delay at 8 and 18 months of corrected postnatal age.

METHODS: During 2008 to 2011, infants at a corrected postnatal age of 8 or 18 months attending health centers in Santiago, Chile, were recruited. Participants completed a form on biographical and demographic characteristics and the Chilean validated version of the Ages and Stages Questionnaires, Third Edition (ASQ). Logistic regression was used to detect the capacity of GA to predict scores $<-2$ SDs on the basis of the Chilean ASQ reference group, in at least 1 ASQ domain, adjusted by different control variables.

RESULTS: A total of 1667 infants were included in the analysis. An inverse “dose response” relationship between developmental delay risk and GA at birth was found, both in the crude and adjusted models. Compared with those born full term, the odds ratio for developmental delay risk was 1.56 for those born early term (95% confidence interval [CI]: 1.19–2.06), 2.58 for infants born late preterm (95%CI: 1.66–4.01), and 3.01 for those born moderately preterm (95%CI: 1.59–5.71).

CONCLUSIONS: An inverse dose-response relationship between GA and risk of developmental delay was found in the tested population. Future prospective studies and predictive models are needed to understand whether this higher developmental risk in moderately and late preterm infants is transient and modifiable or persists throughout life, allowing for better targeting of early-intervention strategies.

WHAT’S KNOWN ON THIS SUBJECT: There is growing evidence reporting that moderately preterm, late preterm, and early term infants are at increased risk of developmental delay. The characteristics of this association are not well established in the literature.

WHAT THIS STUDY ADDS: In a sample of infants born between 32 and 41 weeks, there was an inverse and “dose response” relationship between gestational age and developmental delay risk using the ASQ at 8 and 18 months of corrected postnatal age.
Over the past decades, developed countries have seen a decrease in their natality rates, with a relative increase in births before 40 weeks of gestational age (GA).\(^1,2\) This same trend has occurred in Chile, where total preterm births increased from 5.0% to 6.6% over the past 17 years.\(^3\) This situation can be explained by an increased obstetric risk as a result of late primiparity, an increase in multiple pregnancies, and better pregnancy and labor monitoring techniques.\(^4\)

There has been growing research regarding the risk of moderately preterm (MPT; born by 32\(^0/7\) to 33\(^6/7\) weeks of gestation), late preterm (LPT; 34\(^0/7\) to 36\(^6/7\) weeks), and early term (ET; 37\(^0/7\) to 38\(^6/7\) weeks) children compared with full-term (FT) infants admitted to the NICU and those who were not.\(^5\) A real difficulty in drawing conclusions regarding the impact of delivery before term is the heterogeneity of instruments used and diverse ages of infants at the time of assessments, as well as the fact that most published studies were conducted in retrospective or population-based cohorts.\(^6,7\)

The objective of this study was to evaluate the association between GA at birth and risk of developmental delay at 8 and 18 months of corrected postnatal age by using the Ages and Stages Questionnaires, Third Edition (ASQ).\(^8\) These ages were selected on the basis of Chilean public health guidelines for screening of development in children.\(^9\)

**METHODS**

A cross-sectional study was carried out with the use of a convenience sample of infants aged 8 to 18 months. The ET and FT sample of infants was extracted from the normative sample who participated in the validation study of the ASQ for the Chilean population, which took place between May 2008 and November 2011. In the same time period, MPT and LPT infants were selected by direct contact in health services. Children were recruited from public health centers located in the southeastern and northern districts and from a private eastern center of the metropolitan region of Santiago, Chile.

**Participants**

A convenience sample was constructed on the basis of patients who attended the health center for their routine follow-up visit. Term infants were recruited at scheduled health visits, and preterm infants were identified on the basis of local birth databases in each center and were contacted purposely for the study. Parents or primary caregivers who agreed to participate signed an informed consent and completed a form with medical and biographical and demographic information. GA information was disclosed by the parents and verified with medical records. Infants born at \(\leq36\,6/7\) weeks was corrected by subtracting the weeks remaining to complete 40\(^0/7\) weeks. Infants were classified on the basis of GA as MPT (32\(^0/7\) to 33\(^6/7\) weeks of gestation), LPT (34\(^0/7\) to 36\(^6/7\) weeks of gestation), ET (37\(^0/7\) to 38\(^6/7\) weeks of gestation), or FT (39\(^0/7\) to 41\(^6/7\) weeks of gestation).\(^10\)

Infants aged 7 to 8 months and 30 days and 17 to 18 months and 30 days were included in the study. Each child was tested only once during the study either at 8 or 18 months. The tests were completed on the basis of the appropriated chronological (for FT and ET) or corrected postnatal (for MPT and LPT) ages.

Infants with known genetic, metabolic, or neurologic disease \((n = 14)\); those born at \(<32\,\text{weeks} (n = 10)\); or those born equal at \(\geq42\,\text{weeks} (n = 33)\) were excluded. Those infants without known GA \((n = 54)\) were also excluded. After exclusions, a final sample of 1667 patients was included in the analysis.

**Outcome Measures**

The ASQ is a brief measure in which parents rate their child's current...
skills and development from 1 to 66 months of age. Twenty-one questionnaires are available within this age range. Parents answer 30 questions covering 5 domains of development, including communication, gross motor, fine motor, problem-solving, and adaptive skills. Parents are instructed to try activities with their child to facilitate accurate assessment. A pass/fail score was assigned for each area of development. The presence of any domain that screened $< -2$ SDs below the mean area score for the Chilean reference group was considered to be a positive screen, indicating risk of developmental delay. The ASQ has been validated in several countries.29,30,31 In Chile, the delay. The ASQ has been validated in Chile, and a series of dummy variables were generated for risk of developmental delay in the domains that screened below the mean area score for the Chilean reference group was 75% (95% CI 62%–85%) and 81% (95% CI 76%–86%), respectively, have been reported.32 Parents also completed a form with personal, socioeconomic, demographic, perinatal, and medical information.

**Ethics**

The ethics committees of the National Fund approved this study for Health Research (FONIS), Southwest Santiago Health Service, Southeast Santiago Health Service, and Facultad de Medicina Clinica Alemana-Universidad del Desarrollo.

**Statistical Analysis**

Sample characteristics were described by using the risk frequency for risk of developmental delay in the different GA groups. With the use of data on this criterion, a multivariate-adjusted logistic regression model was constructed. In addition, a series of dummy variables were generated to identify the risk associated with each week of gestation; 40 weeks of GA was used as a reference.

The analysis included the following control variables: socioeconomic status (based on the socioeconomic classification used as a reference for our country),33 teenage mother ($<19$ years old at the time of birth), NICU admission, small for GA (birth weight <10th percentile according to validated tables for Chilean population),34 gender, multiple birth, and ASQ administration age (8 or 18 month). Analyses were performed by using R (Vienna, Austria) and Stata 12 (StataCorp, College Station, TX) platform statistics with a linear trend module.

**RESULTS**

Perinatal and biographical and demographic characteristics of the 1667 participants are shown in Table 1. We observed that the GA distribution of infants evaluated at 8 and 18 months was homogeneous. There was a comparable frequency of teenage pregnancy in all GA groups. In contrast, there was a higher incidence of small for GA, NICU admitted, and multiple births in the preterm infants groups compared with FT group.

A trend toward decreased risk of developmental delay as GA increased was observed (42.86%, 37.58%, and 23.81% for MPT, LPT, and ET, respectively, compared with 17.63% for FT children). An inverse “dose response” relationship between GA and risk of developmental delay was also observed (Fig 1).

When adjusting for predefined variables, the odds of developmental delay risk based on ASQ scores also increased significantly and were inversely related to GA. Compared with those born FT, odds ratios (ORs) were 1.56 (95% confidence interval [CI]: 1.19–2.06) for those born ET, 2.58 (95% CI: 1.66–4.01) for infants born LPT, and 3.01 (95% CI: 1.59–5.71) for those born MPT. The number of affected domains increased as GA decreased. In MPT infants the OR was significant for all domains except for communication. In LPT infants the OR was significant for gross and fine motor domains, whereas for ET infants the OR was significant only in gross motor skills (Table 2). There was a trend for linearity between adjusted risk of developmental delay and GA in the 33- to 40-week interval (Fig 2).

![Graph showing relationship between GA and developmental delay risk](image-url)

**Table 1** Background Characteristics of Participating Children

<table>
<thead>
<tr>
<th>GA Group</th>
<th>MPT (32$^{nd}$ to 36$^{th}$ Weeks)</th>
<th>LPT (34$^{th}$ to 38$^{th}$ Weeks)</th>
<th>ET (37$^{th}$ to 40$^{th}$ Weeks)</th>
<th>FT (39$^{th}$ to 41$^{th}$ Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASQ form, n (%)</td>
<td>8 mo 864 (42.9)</td>
<td>87 (10.1)</td>
<td>274 (31.7)</td>
<td>461 (53.4)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>1667 (81.87)</td>
<td>50 (30.3)</td>
<td>87 (52.7)</td>
<td>10.1 (10.1)</td>
</tr>
<tr>
<td>Socioeconomic status:</td>
<td>1067 (64.0)</td>
<td>10.1 (10.1)</td>
<td>15.9 (15.9)</td>
<td>87 (52.7)</td>
</tr>
<tr>
<td>Adolescent mother, n (%)</td>
<td>1667 (81.87)</td>
<td>10.1 (10.1)</td>
<td>15.9 (15.9)</td>
<td>87 (52.7)</td>
</tr>
<tr>
<td>NICU admission, n (%)</td>
<td>1667 (81.87)</td>
<td>10.1 (10.1)</td>
<td>15.9 (15.9)</td>
<td>87 (52.7)</td>
</tr>
<tr>
<td>Multiple pregnancies, n (%)</td>
<td>1667 (81.87)</td>
<td>10.1 (10.1)</td>
<td>15.9 (15.9)</td>
<td>87 (52.7)</td>
</tr>
<tr>
<td>Small for GA, n (%)</td>
<td>1667 (81.87)</td>
<td>10.1 (10.1)</td>
<td>15.9 (15.9)</td>
<td>87 (52.7)</td>
</tr>
</tbody>
</table>

**Table 2** Results of Logistic Regression Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPT vs FT</td>
<td>1.56 (1.19–2.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LPT vs FT</td>
<td>2.58 (1.66–4.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ET vs FT</td>
<td>3.01 (1.59–5.71)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>


PEDIATRICS Volume 135, number 4, April 2015 e837

Downloaded from http://pediatrics.aappublications.org/ by guest on September 23, 2017
or cubic ($F = 0.16, P = .70$) fit, when compared with linear fit.

When evaluating the effect of each factor isolated from others using univariate analysis, we found associations between risk of developmental delay and GA, NICU admission, multiple pregnancy, and male gender. When controlling for the effects of other predictors using multivariate analysis, GA, male gender, adolescent mother, and ASQ administration age remained significant (Table 3).

### DISCUSSION

We found an inverse, dose-response relationship between corrected GA and risk of developmental delay considering birth at 40 weeks as a reference and after adjusting for predefined control variables. In accordance with our results, previous studies that used the ASQ to identify children at risk of developmental delay found greater developmental delay risk in LPT and MPT infants compared with term infants.8,35

In our study, there was a significant linear inverse relationship between weeks of GA and risk of developmental delay. In addition, no significant improvements were found comparing that adjustment with quadratic or cubic fit. Studies that included extremely preterm children found a linear association between decreasing GA and cognitive development,36,37 whereas others reported an exponential association below 36 weeks by using the ASQ.37 Nevertheless, all studies reported a consistent inverse relationship.13,39–42

The inverse relationship between weeks of GA and frequency of psychomotor problems has a physiologic explanation. It has been described that the last weeks of pregnancy are a critical period for fetal brain development at molecular, neurochemical, and structural levels.43,44 Kugelman and Colin45 presented a descriptive model that combined the pathology that is responsible for preterm delivery and the exposure of the immature brain to the hazards present in the extrauterine environment. Kerstjens et al22 described that LPT infants exposed to neonatal morbidities presented the highest risk of developmental delay. Moreover, the recent data published by Walsh et al21 demonstrated that there is a significant measurable difference in brain size, myelination, and gyral folding between MPT, LPT, and term newborns after correcting for GA at birth, which could potentially explain the differences in development.

In our study, we found high frequencies of risk of developmental delay over all GA groups, comparable to other researchers who used the ASQ.30,46 Those frequencies were higher for 8-month-old children than for 18-month-old children. In the multivariate analysis, the most significant factor for developmental delay risk was ASQ administration age. Other studies conducted by our

---

**TABLE 2** Crude and Adjusted ORs and 95% CIs for Developmental Delay Based on the ASQ

<table>
<thead>
<tr>
<th></th>
<th>MPT (n = 77)</th>
<th>LPT (n = 165)</th>
<th>ET (n = 546)</th>
<th>FT (n = 879)</th>
<th>$\chi^2$ (df = 3)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>3.50</td>
<td>2.15–5.66</td>
<td>2.81</td>
<td>1.95–4.02</td>
<td>1.46</td>
<td>1.13–1.90</td>
</tr>
<tr>
<td>Adjusted</td>
<td>3.01</td>
<td>1.59–5.71</td>
<td>2.58</td>
<td>1.66–4.01</td>
<td>1.56</td>
<td>1.19–2.06</td>
</tr>
<tr>
<td>Communication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>5.39</td>
<td>2.01–13.08</td>
<td>4.23</td>
<td>1.92–9.07</td>
<td>1.11</td>
<td>0.50–2.39</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.50</td>
<td>0.39–5.48</td>
<td>1.53</td>
<td>0.51–4.24</td>
<td>1.05</td>
<td>0.47–2.27</td>
</tr>
<tr>
<td>Gross motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>2.49</td>
<td>1.28–4.54</td>
<td>2.91</td>
<td>1.84–5.22</td>
<td>1.60</td>
<td>1.12–2.27</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.64</td>
<td>1.16–5.88</td>
<td>3.37</td>
<td>1.92–5.88</td>
<td>1.74</td>
<td>1.20–2.52</td>
</tr>
<tr>
<td>Fine motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>2.69</td>
<td>1.38–4.93</td>
<td>1.86</td>
<td>1.09–3.07</td>
<td>1.17</td>
<td>0.79–1.72</td>
</tr>
<tr>
<td>Adjusted</td>
<td>4.28</td>
<td>1.83–9.82</td>
<td>2.55</td>
<td>1.39–4.56</td>
<td>1.24</td>
<td>0.83–1.84</td>
</tr>
<tr>
<td>Problem-solving</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>4.88</td>
<td>2.25–9.96</td>
<td>2.50</td>
<td>1.23–4.83</td>
<td>1.53</td>
<td>0.89–2.61</td>
</tr>
<tr>
<td>Adjusted</td>
<td>2.93</td>
<td>1.03–8.04</td>
<td>1.94</td>
<td>0.83–4.26</td>
<td>1.49</td>
<td>0.85–2.57</td>
</tr>
<tr>
<td>Personal-social</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>4.89</td>
<td>2.39–9.51</td>
<td>3.32</td>
<td>1.84–5.86</td>
<td>1.35</td>
<td>0.81–2.24</td>
</tr>
<tr>
<td>Adjusted</td>
<td>3.31</td>
<td>1.23–8.77</td>
<td>2.00</td>
<td>0.9–4.95</td>
<td>1.49</td>
<td>0.88–2.51</td>
</tr>
</tbody>
</table>

The analysis included the following control variables: socioeconomic status, teenage mother (<19 years old at the time of birth), NICU admission, small for gestational age (birth weight <10th percentile according to validated tables for the Chilean population), gender, multiple birth, and ASQ form. df: degrees of freedom.
FIGURE 2
Trend of ORs for risk of developmental delay based on the ASQ using 40 weeks of GA as the baseline. Note: ORs were adjusted to control the effects of ASQ administration age (8 or 18 month) socio-economic status, teenage mother, NICU admission, small for gestational age, gender, and multiple birth. Higher log ORs indicate higher probability of the presence of developmental delay risk in the child (equal OR: $\chi^2 = 54.69, P < .001$; trend of odds: $\chi^2 = 27.35, P < .001$). Solid line shows trend of ORs for risk of developmental delay and shaded area shows 95% CI trend.

TABLE 3 Univariate and Multivariate Analyses for Risk of Developmental Delay Based on the ASQ

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Fetal and neonatal risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks remaining to 40 weeks of GA</td>
<td>1.21 (1.15–1.28)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>NICU admission</td>
<td>1.87 (1.41–2.48)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Small for GA</td>
<td>1.10 (0.79–1.51)</td>
<td>.573</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>2.65 (1.73–4.03)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.39 (1.11–1.75)</td>
<td>.004</td>
</tr>
<tr>
<td>Other factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>0.64 (0.51–0.81)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Adolescent mother</td>
<td>0.53 (0.36–0.76)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ASQ administration age</td>
<td>3.15 (2.46–4.06)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*Weeks remaining to 40 weeks of GA is included as a continuous variable and ranges from 0 to 8.

group also found a higher frequency of lower ASQ scores in smaller infants, probably associated with parenting practices, with a late catch-up in development. Another significant factor was male gender, which is in accordance with the results of other authors, although there is no a clear explanation of the reason for this difference. Some authors even proposed the use of differentiated norms for boys and girls, but this issue still needs more research.

Unexpectedly, giving birth in adolescence appears to be a protective factor for the risk of developmental delay. Although there is evidence suggesting that teen mothers could be less accurate in identifying developmental delay risk in their children, we believe that these results require further research, including the impact of cultural factors that could affect parenting styles, such as family constitution and family network support for the adolescent mother.

We found it appropriate to correct the GA of MPT and LPT infants both at 8 and 18 months of age on the basis of previous reports. Although currently there are no published data to support correcting GA in ET infants, we believe this is a topic that needs further research. Nevertheless, considering the application guidelines for the ASQ, with a 2-month window for child evaluation, correcting 2 or 3 weeks of age for ET has never changed the recommended application form.

A limitation of this study could be its cross-sectional design. Although the response rate was high, there is no information on the number of eligible children who declined to participate. Because of the nature of the sampling procedure (convenience sampling), the sample is not necessarily representative of the overall population and some GA groups could be over- or underrepresented. It is possible that there was a greater representation of parents/caregivers who were concerned about the health and development of their children, a variable that could be potentially relevant as has been proposed by other researchers.

To increase the knowledge on these associations and to clarify the controversies raised, it is critical to have better prospective studies and predictive models to understand the long-term effect of each developmental risk factor in these populations. Prospective research is necessary for a better understanding of whether the impact of moderate and late prematurity is transient and potentially modifiable or if the differences persist throughout life. Clearly, much research remains to be done in these preterm populations to understand how these differences in development evolve throughout childhood and for better targeting of early-intervention strategies.

ACKNOWLEDGMENTS

We thank Dr Xavier Demestre and Dr Kevin Marks for reviewing and editorial assistance. We also thank Dr Sergio Muñoz for statistical assistance and Dr Andres Maturana for final review and amendment of the final version of the manuscript.
REFERENCES


19. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics. 2011;127(3). Available at: www.pediatrics.org/cgi/content/full/127/3/e622


28. Ministerio de Salud. Normas técnicas de evaluación y estimulación del desarrollo psicomotor en el niño y la niña menor de 6 años [Technical standards of evaluation and stimulation of psychomotor development in boys and girls under 6 years of age]. Santiago


Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants
Luisa Schonhaut, Iván Armijo and Marcela Pérez
Pediatrics 2015;135:e835
DOI: 10.1542/peds.2014-1957 originally published online March 2, 2015;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/135/4/e835

References
This article cites 44 articles, 16 of which you can access for free at:
http://pediatrics.aappublications.org/content/135/4/e835.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Developmental/Behavioral Pediatrics
http://classic.pediatrics.aappublications.org/cgi/collection/developmental_issues_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants
Luisa Schonhaut, Iván Armijo and Marcela Pérez
*Pediatrics* 2015;135:e835
DOI: 10.1542/peds.2014-1957 originally published online March 2, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/135/4/e835