Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants
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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). This same trend has occurred in Chile, where total preterm births increased from 5.0% to 6.6% over the past 17 years. 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.

There has been growing research regarding the risk of moderately preterm (MPT; born by 32/7 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 (39/0/7 to 41/6/7 weeks of gestation) since 2005. These children have a higher risk of short-term perinatal morbidity and long-term developmental, behavioral, and learning difficulties. However, despite the evidence, there is still controversy regarding the actual impact of delivery before the end of gestation. For example, there is debate about the use of corrected postnatal age at the time of assessment of MPT and LPT infants. Woythaler et al showed that LPT infants had a 50% increased risk of developmental delay at a chronological age of 2 years. Romeo et al compared the performance of LPT children at 12 and 18 months, with and without correcting for postnatal age, and found that differences compared with children born FT disappeared after correction. On the other hand, Walsh et al recently showed that a group of MPT and LPT infants had smaller brain size, less myelination, and more immature gyral folding measured by MRI compared with term infants at 38 to 44 weeks’ corrected GA.

Another controversy focuses on the determinants of developmental impact. Some authors have speculated that it could be the result of prematurity, whereas others believe that it is due to associated factors, such as morbidity and NICU admission. Gurka et al reported that healthy LPT infants born after 34/0/7 weeks, without neonatal complications, had long-term cognition, achievement, socioemotional, and behavioral development equivalent to FT infants. Baron et al found lower performance in infants with complicated LPT birth compared with those with uncomplicated birth. This hypothesis has been discredited by MacGowan et al, who found no significant differences in early childhood development between LPT infants admitted to the NICU and those who were not.

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. 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). These ages were selected on the basis of Chilean public health guidelines for screening of development in children.

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 validity 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. The chronological age of infants born at ≤36/6/7 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).

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 weeks (n = 10); or those born equal at ≥42/0/7 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. In Chile, the sensitivity and specificity ranges of 75% (95% CI 62%–85%) and 81% (95% CI 76%–86%), respectively, have been reported. 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), 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), gender, multiple birth, and ASQ administration age (8 or 18 month). Analyses were performed by using R (Vienna, Austria) and Stata 12 (StatCorp, 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). The χ2 for trend of ORs was 27.33 (P < .001). An evaluation for adjustment of linear trend of the relation between GA and development delay risk was significant (F = 81.87, P < .001, R2 = 0.90) and no significant improvements in adjustment were found for quadratic (F = 3.19, P = .11).

### TABLE 1 Background Characteristics of Participating Children

<table>
<thead>
<tr>
<th>GA Group</th>
<th>MPT (33\textsuperscript{rd} to 36\textsuperscript{th} Weeks)</th>
<th>LPT (34\textsuperscript{th} to 36\textsuperscript{th} Weeks)</th>
<th>ET (37\textsuperscript{rd} to 38\textsuperscript{th} Weeks)</th>
<th>FT (39\textsuperscript{rd} to 41\textsuperscript{st} Weeks)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASQ form, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.799</td>
</tr>
<tr>
<td>8 mo</td>
<td>864</td>
<td>42 (4.9)</td>
<td>87 (10.1)</td>
<td>274 (31.7)</td>
<td>461 (53.4)</td>
</tr>
<tr>
<td>18 mo</td>
<td>863</td>
<td>35 (4.4)</td>
<td>78 (8.7)</td>
<td>272 (32.1)</td>
<td>418 (51.2)</td>
</tr>
<tr>
<td>Total</td>
<td>1667</td>
<td>77 (4.6)</td>
<td>165 (9.7)</td>
<td>546 (32.7)</td>
<td>879 (52.8)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.034</td>
</tr>
<tr>
<td>1667</td>
<td>48 (2.9)</td>
<td>89 (53.9)</td>
<td>258 (47.3)</td>
<td>416 (47.3)</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status: medium-low vs. medium-high, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>1667</td>
<td>43 (55.8)</td>
<td>70 (42.4)</td>
<td>363 (66.5)</td>
<td>591 (67.2)</td>
<td></td>
</tr>
<tr>
<td>Adolescent mother, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.154</td>
</tr>
<tr>
<td>1667</td>
<td>9 (11.7)</td>
<td>15 (9.1)</td>
<td>81 (14.8)</td>
<td>137 (15.6)</td>
<td></td>
</tr>
<tr>
<td>NICU admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1667</td>
<td>72 (43.3)</td>
<td>87 (52.7)</td>
<td>59 (10.8)</td>
<td>61 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancies, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1667</td>
<td>36 (46.8)</td>
<td>46 (27.9)</td>
<td>11 (2.0)</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Small for GA, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1655</td>
<td>30 (39.0)</td>
<td>50 (37.2)</td>
<td>64 (41.9)</td>
<td>88 (10.1)</td>
<td></td>
</tr>
</tbody>
</table>
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).

### TABLE 2

<table>
<thead>
<tr>
<th>Total</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>MPT (n = 77)</th>
<th>LPT (n = 165)</th>
<th>ET (n = 546)</th>
<th>FT (n = 879)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>3.50 (2.15–5.66)</td>
<td>3.01 (1.59–5.71)</td>
<td>2.81 (1.95–4.02)</td>
<td>1.46 (1.13–1.90)</td>
<td>1.00 (1.13–1.90)</td>
<td>1.00 (1.13–1.90)</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.81–5.66</td>
<td>1.59–5.71</td>
<td>1.95–4.02</td>
<td>1.13–1.90</td>
<td>1.00–1.90</td>
<td>1.00–1.90</td>
</tr>
</tbody>
</table>

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

**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 extraterine 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...
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.

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