Pain Sensitivity in Prematurely Born Adolescents

Dan Buskila, MD; Lily Neumann, PhD; Ehud Zmora, MD; Marina Feldman, MD; Arkady Bolotin, PhD; Joseph Press, MD

Background: Several studies reported that preterm infants were found to be hypersensitive to pain. However, longitudinal and quantitative assessments of subsequent pain thresholds in adolescence are scarce.

Objective: To assess the tenderness threshold in adolescents born prematurely compared with matched children born at full term.

Design: Case-control study.

Setting: Children in the community recruited from the files of the neonatal intensive care unit.

Participants: Sixty adolescents (aged 12-18 years) born prematurely and 60 adolescents born at full term.

Main Outcome Measures: Tenderness thresholds were assessed by tender-point count and by dolorimeter.

Results: The preterm-born children had significantly more tender points (6.0±5.2 vs 3.3±3.3; P=.001) and lower tender thresholds (4.2±1.5 vs 4.8±1.6 kg; P=.04), measured by a dolorimeter, than children born at full term. In both groups, girls had significantly more tender points and lower tender thresholds. Despite their increased tenderness, most of the preterm children did not report pain or other related symptoms.

Conclusions: The fact that preterm-born children and adolescents display higher somatic pain sensitivity may be of relevance to physicians taking care of these children, since they may be prone to developing pain syndromes in the future. Further follow-up studies are needed to confirm this hypothesis.


THERE ARE consistent data that preterm infants have a lower threshold to tactile stimulation and appear to be hypersensitive to pain. Grunau et al reported that children of extremely low birth weight who had experienced lengthy stays in the neonatal intensive care unit in infancy showed, at the age of 4 to 5 years, significantly higher somatization, ie, somatic complaints of unknown origin, compared with children who had been full-term, healthy neonates. The emotional and behavioral adjustment of 13-year-old children born pretermly was found to be lower than that of children born full term.

Repetitive pain in neonatal rat pups led to an altered pain system associated with decreased pain thresholds during development. Since human preterm neonates are subjected to repetitive pain during prolonged periods of neonatal intensive care, it was hypothesized that this may cause permanent behavioral changes in pain perception during later childhood of preterm-born infants.

However, few longitudinal studies have examined the effects of early pain on subsequent pain responses in childhood and adolescence. Specifically, even fewer studies have quantitatively assessed the pain thresholds of preterm-born children by directly assessing the children, and not by interviewing their parents.

Evaluating tenderness is important because of its relationship to pain syndromes. Increased tenderness is associated with disabling chronic pain syndromes, such as fibromyalgia. The aim of the present controlled study was to quantitatively assess the tenderness threshold in adolescents born prematurely compared with matched children born at full term.

METHODS

SUBJECTS

The study population consisted of 60 Israeli children born prematurely at very low birth weight (preterm group) and 60 children born at full term (full-term control group).
The preterm group was recruited through the files of the neonatal intensive care unit in Soroka Medical Center, Beer Sheva, Israel, between January 1, 1982, and December 31, 1989. Sixty children (of a list of 75) could be located for the present study. The hospital serves as a tertiary referral center for the southern part of Israel. The current ages of the study population were limited to a range of 11 to 18 years, to ensure their compliance. The criteria for selection of the preterm-born children were birth weight equal to or less than 1500 g and gestational age less than 35 weeks.

For the full-term children, the criterion for selection was gestational age greater than or equal to 37 weeks, and a normal course of pregnancy and birth. The full-term children were matched with the preterm children by age and were selected among their friends. The sex ratio in both groups was similar.

All children and their parents were interviewed by means of a structured questionnaire for demographic data and birth-related information. Medical data were verified with the records from the neonatal intensive care unit.

The study was approved by the Helsinki Ethics Committee of the Soroka Medical Center. One parent of each child gave a written consent after having received detailed information about the study.

TENDERNESS ASSESSMENT

In all subjects, 18 tender points were counted by thumb palpation. These points were suggested (by the American College of Rheumatology) for assessing nonarticular tenderness in studies of widespread pain and fibromyalgia.8

Thirteen point sites (9 tender point-sites and 4 control point sites) were further studied with a dolorimeter. The 9 tender-point sites consisted of 5 sites on the right and 2 sites on both sides. These were trapezius (right and left), midpoint of the upper fold; occiput (right) below occipital prominence; cervical spine (right), anterior aspect of intertransverse space at C5-7; second c Abbreviations: NA, not applicable; NICU, neonatal intensive care unit.

Table 1. Background Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preterm (n = 60)</th>
<th>Full-Term (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14.1 (1.7)</td>
<td>13.9 (1.7)</td>
<td>.61</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>24.36</td>
<td>27.33</td>
<td>.58</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1232 (177)</td>
<td>3491 (265)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>31.4 (2.1)</td>
<td>38.8 (1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time in NICU, d</td>
<td>64.9 (43.3)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Mother’s age at delivery, y</td>
<td>28.0 (5.2)</td>
<td>29.4 (2.9)</td>
<td>.09</td>
</tr>
<tr>
<td>Mother’s education, y</td>
<td>12.5 (2.9)</td>
<td>12.9 (1.9)</td>
<td>.38</td>
</tr>
<tr>
<td>Father’s education, y</td>
<td>12.2 (2.7)</td>
<td>12.4 (1.2)</td>
<td>.63</td>
</tr>
</tbody>
</table>

Table 2. Measures of Tenderness in Preterm and Full-Term Children

<table>
<thead>
<tr>
<th>Measure (Range)</th>
<th>Preterm (n = 60)</th>
<th>Full-Term (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tender points (1-18)</td>
<td>6.0 (5.2)</td>
<td>3.3 (3.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Dolorimeter threshold, kg (range 0-9)</td>
<td>4.2 (1.5)</td>
<td>4.8 (1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Mean at 9 tender points</td>
<td>6.3 (1.8)</td>
<td>7.0 (1.5)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Table 3 displays measures of tenderness in preterm and full-term children by sex. The results in boys and girls are presented separately because previous find-
ings have shown consistently that females are more tender than males. Indeed, in both groups, girls had significantly more tender points and lower tender thresholds. Thus, the difference between preterm and full-term children remained significant even after controlling for sex.

PAIN AND RELATED SYMPTOMS

The prevalence and severity of pain and other related symptoms (stiffness, fatigue, and sleep problems) were assessed in both groups. Most of the children did not report any complaints. Specifically, only 1 prematurely born child reported pain and stiffness. Fatigue and anxiety were reported by preterm subjects only: 8 of them (13%) reported fatigue, and 5 (8%), anxiety.

BIRTH INFORMATION AND MEASURES OF TENDERTNESS

In preterm subjects, a moderate association was observed between birth weight and tenderness thresholds ($r = 0.28, P = .03$) and number of tender points ($r = 0.22, P = .10$). No such relationship was shown for full-term children ($r = 0.18, P = .16$; and $r = -0.05, P = .70$, respectively). Interestingly, despite a strong correlation between birth weight and gestational age in preterm children ($r = 0.51, P < .001$), the latter was not correlated with tenderness measurements.

Twenty (33%) of 60 preterm children had received mechanical ventilation as newborns. There were no differences between their tenderness measurements and those of the children who did not receive ventilation.

The prematurely born infants had stayed in the neonatal intensive care unit for 30 to 300 days (mean, 65 days). The length of stay was not found to be correlated with tenderness.

Our study demonstrated increased tenderness at tender point sites and control sites in prematurely born adolescents compared with full-term children. The increased tenderness in the preterm group was observed in both sexes. In each group (preterm and full-term), the girls displayed higher pain sensitivity than the boys. This finding is in accordance with previous studies demonstrating greater tenderness in females than in males, both in children and in adults. Similar sex differences have recently been reported regarding neonates. Despite the somatic hypersensitivity in our preterm group, most of them did not report pain and related symptoms.

Our findings confirm the results of previous studies regarding somatic hypersensitivity in prematurely born children. However, those studies have assessed pain responses in preterm children by means of tactile stimulation or parental report. The ages of the children have ranged from infancy to 4.5 years. Later emotional and behavioral adjustment of 13-year-old children born prematurely was assessed and compared with that in full-term children. Thus, studies examining the long-term effects of early pain in prematurity on subsequent pain are limited. In contrast to previous studies, we have assessed tenderness in older preterm-born children (aged 12-18 years) by means of quantitative measures of pain response, namely, tender-point count and dolorimetry thresholds. The methods of assessment proved to be reliable in children of comparable ages.

The perception of pain in preterm infants is thought to be slightly different from that of term infants, because of a lack of myelination of their sensitive fibers and a still immature cortical organization of the somatosensory system. Thus, painful stimuli are perceived to be more widespread and durable. In addition, the threshold of pain seems to be lower in premature infants, probably due to a lack of protection of their spinal and supraspinal inhibitory pathways. Furthermore, abnormal behavioral imprinting secondary to early painful stimuli is suggested. Indeed, preterm neonates are subjected to repetitive pain during neonatal intensive care. It has recently been shown that repetitive pain in neonatal rat pups may lead to an altered development of the pain system associated with decreased pain thresholds during development. Increased plasticity of the neonatal brain may result in future increased vulnerability of the central nervous system to stress and pain disorders.

The recognition of potentially altered pain sensitivity in prematurely born children is relevant to physicians taking care of them, since it may explain exaggerated pain response to various stimuli.

It is important to follow up these preterm-born children, since one would predict that these tender subjects would be more likely to develop pain syndromes in future years than the nontender full-term–born subjects. In addition, the long-term consequences of pain in early life associated with mechanical trauma should be evaluated in prospective longitudinal studies.
What This Study Adds

Although several studies reported that preterm infants were found to be hypersensitive to pain, longitudinal and quantitative assessments of subsequent pain thresholds in adolescents are scarce.

This study demonstrates increased tenderness at tender point sites in prematurely born adolescents compared with full-term children. This is the most comprehensive controlled study in this age group, using quantitative assessment of pain thresholds. The recognition of potentially altered pain sensitivity in prematurely born children is relevant to physicians taking care of them, since it may explain exaggerated pain response to various stimuli.

Accepted for publication March 7, 2003.
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REFERENCES