Elevation of Uterine Basal Tone and Fetal Heart Rate Abnormalities After Labor Analgesia
A Randomized Controlled Trial

Karen Cristine Abrão, MD, PhD, Rossana Pulcinelli Vieira Francisco, MD, PhD, Seizo Miyadahira, MD, PhD, Domingos Dias Cicarelli, MD, PhD, and Marcelo Zugaib, MD, PhD

OBJECTIVE: To estimate the effects of combined spinal–epidural and traditional epidural analgesia on uterine basal tone and its association with the occurrence of fetal heart rate (FHR) abnormalities.

METHODS: Seventy-seven laboring patients who requested pain relief during labor were randomly assigned to combined spinal–epidural (n=41) or epidural analgesia (n=36). Uterine contractions and FHR were recorded 15 minutes before and after analgesia. Uterine tone was evaluated with intrauterine pressure catheter. Primary outcomes were the elevation of baseline uterine tone and occurrence of FHR prolonged decelerations or bradycardia after analgesia. The influence of other variables such as oxytocin use, hypotension, and speed of pain relief were estimated using a logistic regression model.

RESULTS: The incidence of all outcomes was significantly greater in the combined spinal–epidural group compared with epidural: uterine hypertonus (17 compared with 6; P=.018), FHR abnormalities (13 compared with 2; P<.01), and both events simultaneously (11 compared with 1; P<.01). Logistic regression analysis showed the type of analgesia as the only independent predictor of uterine hypertonus (odds ratio 3.526, 95% confidence interval 1.21–10.36; P=.022). For the occurrence of FHR abnormalities, elevation of uterine tone was the independent predictor (odds ratio 18.624, 95% confidence interval 4.46–77.72; P<.001). Regression analysis also found a correlation between decrease on pain scores immediately after analgesia and the estimated probability of occurrence of hypertonus and FHR abnormalities.

CONCLUSION: Combined spinal–epidural analgesia is associated with a significantly greater incidence of FHR abnormalities related to uterine hypertonus compared with epidural analgesia. The faster the pain relief after analgesia, the higher the probability of uterine hypertonus and FHR changes.


LEVEL OF EVIDENCE: I

Fetal heart rate (FHR) abnormalities after labor analgesia are a daily challenge for obstetricians and anesthesiologists and a concern for patients who desire to have pain relief during childbirth.1,2 Despite great popularization of regional analgesia for labor, the causes and management of these abnormalities still remain controversial.

The increasingly popular combined spinal–epidural technique with addition of opioids has been associated in various studies with a higher incidence of nonreassuring FHR tracings, and its possible causes still have no scientific confirmation.3,4 One of the hypotheses to explain it is that the effective and rapid onset pain relief provided by that method can cause a transient imbalance in maternal catecholamine level, leading to uterine hyperactivity. This hyperactivity could submit the fetus to a stress test, resulting in the observed abnormalities on fetal heart rate tracings.5,6 To date, this hypothesis has been assessed by some authors, but most studies used external tocography or clinical evaluation of uterine activity. No study has evaluated the hypothesis using internal
monitoring and a randomized design, comparing the combined spinal–epidural technique with another regional type of analgesia as the traditional epidural. The aim of the present study was to estimate the effects of combined spinal–epidural and traditional epidural analgesia on the uterine basal tone and its association with the occurrence of FHR abnormalities.

PATIENTS AND METHODS

We prospectively evaluated 77 low-risk laboring patients, who were randomly assigned to receive one of two labor analgesia techniques: combined spinal–epidural group or traditional epidural group. All patients were followed during labor at the University Hospital, São Paulo University, Brazil, between April 2006 and March 2007. The study was approved by the Institutional Review Board of the University Hospital, São Paulo University, and written informed consent for participation was obtained from each patient.

Patients were admitted to the study at their first request for regional analgesia, if they met inclusion criteria and did not have any exclusion criteria. Admission criteria were singleton, cephalic, full-term pregnancies, request for analgesia before 7 cm of cervical dilatation. Exclusion criteria were contraindications to regional analgesia, previous use of systemic opioids for labor pain relief, cervical ripening with prostaglandins, amniotic infection, and maternal or fetal known medical conditions.

Study subjects were monitored with an intrapartum pressure transducer, Intran Plus IUP-400 (Utah Medical Products Inc., Midvale, UT), for at least 15 minutes before and 15 minutes after labor analgesia. The intrapartum pressure device was inserted after rupture of membranes. Assisted rupture was performed beyond 3 cm of cervical dilatation. All catheters were placed by the same researcher (K.C.A.). Fetal heart rate was monitored with an external transducer.

Pain was evaluated using a visual analogue scale (VAS) of 10 cm, with 0 corresponding to feeling no pain and 10 cm corresponding to the worst pain imaginable. It was assessed when the patient requested analgesia and every 5 minutes after analgesia induction, for 20 minutes.

Women admitted to the study were assigned to groups using computer-generated random series produced by a person not related to the protocol. The anesthesiologist who performed the procedure received the next in a numbered series of sealed opaque envelopes containing the protocol’s instructions. The type of analgesia in each patient was unknown to the patient or the obstetric team (which included the obstetrician responsible for labor assistance and the one responsible for data gathering). To accomplish blinding, only the anesthesiologist and the nurse remained in the operating room during the anesthetic procedure. The type of analgesia was not revealed until the end of the study.

All women received prehydration with 10 mL/kg lactated Ringer’s solution or normal saline. Patients in the combined spinal–epidural group received intrathecal solution of 0.5% bupivacaine 2.5 mg plus 2.5 micrograms sufentanil, followed by placement of an epidural catheter with needle-through-needle technique. Patients in the epidural group received epidural injection of 0.125% bupivacaine 12.5 mg plus sufentanil 10 micrograms, followed by placement of the epidural catheter. Analgesia was maintained with subsequent epidural boluses upon patient request, with doses according to cervical dilatation: 0.125% until 7 cm, 0.25% between 8 and 9 cm, and 0.5% in the second stage. No epidural boluses were administered in the first 20 minutes of analgesia induction.

Cardiotocographic records were later analyzed by two maternal–fetal specialists blinded to the group to which each patient belonged. If there was any disagreement in their evaluation, tracings were reviewed until consensus was obtained. Tracings were searched for FHR abnormalities and for the occurrence of an elevation of basal uterine tone after analgesia compared with the values prior to analgesia.

Primary outcomes were the occurrence of prolonged decelerations or bradycardia of the FHR and the increase of 10 mm Hg or more in basal uterine tone after analgesia. Prolonged deceleration was defined as a fall of 15 beats per minute or more in the baseline of the fetal heart rate lasting more than 2 minutes and less than 10 minutes. Fetal bradycardia was defined as the fall of baseline to less than 100 bpm. The analysis was performed for the first 15 minutes of analgesia induction, because these alterations seem to occur very rapidly with combined spinal–epidural analgesia.

Secondary outcome was the occurrence of maternal hypotension after analgesia induction, defined as systolic blood pressure less than 100 mm Hg or 20% decrease from baseline, measured by automated monitor before analgesia and every 5 minutes afterward.

Cases were managed according to the common practice of the University Hospital obstetric team, and oxytocin use was allowed and recorded. If the patient was using oxytocin before analgesia, the dose was...
maintained the same during the first 15 minutes of analgesia, and no oxytocin was first introduced in the interval before analgesia or the first 15 minutes after. Cases presenting FHR abnormalities could have oxytocin suspended if there was any evidence of uterine hyperactivity.

Other variables studied included maternal characteristics (age, parity, and gestational age); VAS at analgesia request and every 5 minutes after analgesia; labor progress before analgesia induction (cervical dilatation, fetal head station, use and dose of oxytocin), mode of delivery, and immediate neonatal outcomes (Apgar scores, umbilical artery pH at birth).

Sample size was calculated to detect a clinically relevant difference of 10 mm Hg in uterine basal tone before and after analgesia with a 30% difference in both groups, a statistical power of 85%, and a significance level of 5%. The 30% difference between groups was estimated from a previous pilot study with 18 patients. Sample size was estimated to be 70 patients, 35 per group. Considering a maximal 20% loss, we needed to assign 84 parturients to the groups.10

All of the above-mentioned variables were submitted to comparative studies, performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL). The χ² and Fisher exact tests were used for dichotomous data. Continuous data were analyzed with Student t test or Mann–Whitney U test.11 Statistical significance was assumed if P<.05. Regression analysis was performed with a logistic regression model to identify the possible influence of maternal hypotension and oxytocin use on the studied outcomes. The effect of pain relief after analgesia on the occurrence of FHR abnormalities related to uterine tone elevation was also estimated using logistic regression.12

RESULTS

The initial sample consisted of 91 patients. Subsequently, 14 of these patients were excluded due to the impossibility of maintaining adequate cardiotocographic records (n=11), evolution to delivery in less than 30 minutes (n=2), or failure in anesthetic puncture (n=1). The final sample thus included 77 laboring patients, 41 in the combined spinal–epidural group and 36 in the epidural group (Fig. 1).

Table 1. Maternal Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CSE Group (n=41)</th>
<th>EPI Group (n=36)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>23.95±5.99</td>
<td>23.61±6.84</td>
<td>.55</td>
</tr>
<tr>
<td>Gestational Age (wk)</td>
<td>39.46±1.42</td>
<td>39.50±1.15</td>
<td>.78</td>
</tr>
<tr>
<td>Dilatation at analgesia</td>
<td>5.71±0.75</td>
<td>5.58±0.84</td>
<td>.46</td>
</tr>
<tr>
<td>Fetal head station at</td>
<td>−1.54±1.02</td>
<td>−1.83±0.88</td>
<td>.25</td>
</tr>
<tr>
<td>analgesia</td>
<td>−2</td>
<td>−2</td>
<td></td>
</tr>
<tr>
<td>VAS score at analgesia</td>
<td>8.59±1.22</td>
<td>8.7±1.14</td>
<td>.72</td>
</tr>
<tr>
<td>Dose of oxytocin</td>
<td>4.10±5.42</td>
<td>4.36±3.91</td>
<td>.25</td>
</tr>
</tbody>
</table>

CSE, combined spinal–epidural; EPI, epidural; SD, standard deviation; IQR, interquartile range; VAS, visual analog scale.

*P values from the Mann-Whitney U test.
Maternal characteristics are presented in Table 1, with no significant differences between groups. Most patients were nulliparous, 63.4% (26 of 41) in the combined spinal–epidural group and 75% (27 of 36) in the epidural group (P= .27). Table 2 presents the analysis of outcomes for uterine tone, FHR abnormalities, and maternal hypotension after analgesia induction in the two groups. Of the 13 (31.7%) women who presented FHR abnormalities during the first 15 minutes of analgesia in the combined spinal–epidural group, seven had bradycardia, and six had prolonged decelerations. In the epidural group, only two patients had FHR abnormalities, one prolonged deceleration and one bradycardia. Statistical analysis revealed significant differences between groups, with combined spinal–epidural patients presenting a higher proportion of episodes of uterine tone elevation and FHR abnormalities after analgesia. Eleven patients in the combined spinal–epidural group had simultaneous FHR abnormalities and hypertonus, and in the epidural group only one patient did (P<.01). Table 2 also shows that maternal hypotension was present in only few cases that presented FHR abnormalities, with no difference between groups (P= .49).

All cases had resolution of the hypertonus and nonreassuring fetal heart rate with general measures, such as hydration, suspension of oxytocin (if it was in use before analgesia), and oxygen supplementation. No cases needed tocolysis, and no emergency cesarean delivery was performed for suspected fetal distress.

The mean pain relief on VAS was higher in the combined spinal–epidural group at all evaluations until 20 minutes of analgesia. At 5 minutes, the combined spinal–epidural group had a mean±standard deviation decrease in VAS scores of –6.3±2.6 cm compared with –4.1±2.8 cm in the epidural group, at 10 minutes –7.3±2.2 cm compared with –5.2±2.6 cm, and at 15 minutes –7.7±1.9 cm compared with –6.1±2.5 cm. Repeated-measures analysis of variance was used to estimate the differences in pain scores just before and every 5 minutes after analgesia between groups. Both groups had a significant reduction in pain scores across time, and the time-by-treatment interaction (mode of analgesia) showed lower pain scores in the combined spinal–epidural group compared with epidural group (F_{105}=14; P<.001).

Neonatal results were similar between groups, with no cases presenting umbilical artery pH less than 7.00 or 5-minute Apgar scores less than 7 in any group. There was also no difference between the combined spinal–epidural and epidural group in the incidence of cesarean delivery (31.7% compared with 36.1%, P=.68).

After univariable analysis, we performed a logistic regression model of data to exclude possible interference in the results (Table 3). The selection of variables was made on the basis of clinical relevance. Increases of 10 mm Hg or more in baseline uterine tone occurred in 23 cases, and the variables chosen were mode of analgesia and dose of oxytocin at

### Table 2. Evaluation of Uterine Tone, Fetal Heart Rate Abnormalities, and Maternal Hypotension in the First 15 Minutes After Analgesia According to Group

<table>
<thead>
<tr>
<th>Outcomes After Analgesia</th>
<th>CSE Group (n=41)</th>
<th>EPI Group (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine tone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>24 (58.5)</td>
<td>30 (83.3)</td>
<td>.018*</td>
</tr>
<tr>
<td>Elevated</td>
<td>17 (41.5)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>28 (68.3)</td>
<td>34 (94.4)</td>
<td>&lt;.01†</td>
</tr>
<tr>
<td>Abnormal</td>
<td>13 (31.7)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>FHR abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with hypertonus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30 (73.2)</td>
<td>35 (97.2)</td>
<td>&lt;.01†</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (26.8)</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>FHR abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>39 (95.1)</td>
<td>36 (100)</td>
<td>.49†</td>
</tr>
</tbody>
</table>

CSE, combined spinal–epidural; EPI, epidural; FHR, fetal heart rate.

Data are n (%).

* P values from the χ² test.

† P values from the Fisher exact test.

### Table 3. Results of the Logistic Regression Models for Each Outcome and the Respective Odds Ratio and 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation of uterine tone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSE vs epidural</td>
<td>3.526</td>
<td>1.21–10.36</td>
<td>.022</td>
</tr>
<tr>
<td>Oxytocin dose</td>
<td>0.981</td>
<td>0.88–1.09</td>
<td>.719</td>
</tr>
<tr>
<td>FHR abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevation of uterine tone after analgesia</td>
<td>18.624</td>
<td>4.46–77.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postblock hypotension</td>
<td>0.561</td>
<td>0.09–3.57</td>
<td>.541</td>
</tr>
<tr>
<td>FHR abnormalities with elevation of uterine tone</td>
<td>0.772</td>
<td>0.59–0.99</td>
<td>.049</td>
</tr>
<tr>
<td>Decrease in pain scores 5 min after analgesia</td>
<td></td>
<td></td>
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</tbody>
</table>

CI, confidence interval; CSE, combined spinal–epidural; FHR, fetal heart rate.
analgesia induction. These variables were selected to enter the model for their clinical relevance and consideration of the number of outcome events. Uterine hypertonus occurred in 16.7% (6) of epidural group compared with 41.7% (17) in the combined spinal–epidural group ($P=.018$). Mean±standard deviation oxytocin dose was $4.4±4.3$ milliunits/min in the normal tone group, with a median of 4 milliunits/min (range 0–16). In the elevated tone group, mean dose was $3.9±5.7$ milliunits/min, and the median dose was 2 milliunits/min (range 0–24). The Mann-Witney $U$ test revealed no difference between groups in relation to oxytocin ($P=.302$). Despite the univariable results, oxytocin was maintained in the model, to estimate its influence in the occurrence of uterine hypertonus. After the analysis of the model, the only variable independently predicting the elevation of baseline tone was the mode of analgesia, with combined spinal–epidural group odds ratio (OR) of 3.526 (95% confidence interval [CI] 1.21–10.36; $P=.022$).

To predict the occurrence of fetal heart rate abnormalities, the variables selected were the occurrence of uterine tone elevation and maternal hypotension. Both variables were selected based on clinical relevance to estimate their effect on the occurrence of FHR abnormalities. There were 15 cases for that analysis, 13 from combined spinal–epidural group and two from epidural group. Uterine hypertonus occurred in 12 of 15 (80%) patients presenting FHR changes and 11 of 62 (17.7%) with normal FHR tracings ($P<.001$). Maternal hypotension was present in 2 of 15 (13.3%) patients with nonreassuring FHR tracings and 13 of 62 (21%) with normal FHR tracings ($P=.72$). After regression analysis, the only independent predictor of the occurrence of nonreassuring FHR tracings was the elevation of uterine tone, with an OR of 18.624 (95% CI 4.46–77.72; $P<.001$).

Considering the 12 cases in which elevation of uterine tone was present along with FHR abnormalities (one from the epidural group and 11 from the combined spinal–epidural group), the calculated number needed to harm was 4.2 (95% CI 2.6–10.2) patients, meaning that in almost every four patients receiving combined spinal–epidural analgesia, one would have FHR abnormalities associated with elevation of uterine tone.

We also used a logistic regression model to estimate the effect of pain relief as a predictor of fetal heart rate abnormalities associated with uterine hypertonus in the cases that had both outcomes. The mean VAS decrease in the first 5 minutes of analgesia induction was higher in the group that had FHR abnormalities associated with simultaneous uterine tone elevation ($-6.83±2.12$ cm compared with $-4.98±2.9$ cm, $P=.041$). After the analysis of the model, decrease in VAS was an independent predictor of the occurrence of FHR abnormalities simultaneous with uterine hypertonus (OR 0.772, 95% CI 0.598–0.998). Figure 2 and Figure 3 demonstrate the predicted probabilities of FHR abnormalities associated with uterine hypertonus according to the 5-minute VAS decrease after analgesia, showing that the faster the pain relief, the higher the probability of elevation of uterine tone and coincident FHR changes.

**DISCUSSION**

The present study tested the hypothesis that combined spinal–epidural analgesia is associated with elevation of baseline uterine tone and fetal heart rate abnormalities when compared with the traditional epidural. We observed a transient elevation of uterine tone in almost one half of the patients after induction of this type of labor analgesia (17 of 41). Among patients who presented an elevation of uterine tone of more than 10 mm Hg, almost 64.5% (11 of 17) had simultaneous FHR abnormalities in the first 15 minutes of injection. Compared with the traditional epidural, the elevation of uterine tone in the same period...
occurred in only six of 36 (16.7%) of patients, and one of six (16.7%) of fetuses had simultaneous bradycardia.

The results presented support the pathophysiology proposed by Cohen et al\(^5\) that the rapid onset of analgesia with combined spinal–epidural is involved in the occurrence of uterine hypertonus and fetal bradycardia. Effective pain relief causes a significant decrease in maternal circulating catecholamines, especially epinephrine. The tocolytic effect of epinephrine can be lost, with predominance of norepinephrine’s uterotonic effect. The resulting imbalance may lead to hypertonus and subsequent FHR abnormalities. All effective labor analgesia techniques can decrease epinephrine concentrations; however, a previous study\(^13\) had already confirmed that it happens faster with combined spinal–epidural using opioids compared with epidural, notably in the first 5 minutes of analgesia. Norepinephrine levels had minimal changes in both groups in that study. We did not obtain maternal catecholamine levels from our patients, but the estimated probability of occurrence of uterine hypertonus and FHR abnormalities was higher among patients with intense pain relief immediately after the block. These findings strengthen the evidence that the speed of pain relief is involved in the FHR abnormalities seen after combined spinal–epidural analgesia.

In a recent publication, Nicolet et al\(^14\) reported an association between maternal pain scores before analgesia and the occurrence of FHR changes after combined spinal–epidural or epidural. However, that study was not randomized, and differences in speed of pain relief were not reported. The authors assumed that the differences in previous pain scores could be credited to the selection of patients, ie, women with greater pain would have more chance to receive combined spinal–epidural analgesia, which could influence the incidence of FHR changes. In our study, the randomization allowed us to include patients with similar pain scores before analgesia in both groups, eliminating that bias. Our results suggest that the speed of pain relief after analgesia is probably mainly responsible for those changes.

Our findings also suggest that the occurrence of uterine hypertonus is even more frequent than observed in previous studies. The explanation for the apparent divergent results from previous authors is probably the more accurate analysis of uterine activity, with internal monitoring, used in the present evaluation.\(^4,6\)

Van de Velde et al\(^4\) reported 12% FHR abnormalities with only 2% uterine hyperactivity in the group receiving bupivacaine with sufentanil and no difference in comparison with the epidural group (11% FHR abnormalities and 2% uterine hyperactivity). In the group receiving intrathecal sufentanil exclusively, the incidence of FHR was higher (24%), with 12% associated uterine hyperactivity. This study, however, had evaluated uterine hypertonus with external tocography and/or uterine manual palpation.

Vercauteren et al\(^6\) reported a study with internal uterine monitoring, showing association between fetal bradycardia and an increase in uterine basal tone among patients receiving intrathecal opioids. They reported seven cases of cardiotocographic changes among 25 patients who received intrathecal sufentanil 5 micrograms and 1 mg bupivacaine, and two of them had simultaneous uterine tone elevation. However, they did not compare the groups with epidural opi-

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**Fig. 3.** Probability of fetal heart rate abnormalities with uterine hypertonus after analgesia according pain relief in the first 5 minutes as measured by the visual analog scale. The solid line represents the linear regression, with an estimated probability of 0.00 + 0.03x (change in visual analog scale scores from before analgesia to 5 minutes after analgesia); the dotted lines show the 95% confidence interval; the dashed lines show the 95% prediction interval. VAS, visual analog scale.

oids, and evaluation of FHR abnormalities was not the primary outcome.

We chose to use epidural analgesia as the control group in the present study for its similar efficacy with combined spinal–epidural technique and because it is the standard treatment of labor pain.\textsuperscript{15} We also limited the inclusion of patients to those receiving analgesia before 7 cm of cervical dilatation to make groups more comparable. Analgesia induction in more advanced labor would require the epidural group to have higher doses of anesthetics, jeopardizing comparison of the techniques. Furthermore, to start analgesia in the second stage of labor would bring about confusion bias with fetal heart rate abnormalities characteristic to this period. The choice of drugs and doses used were also made based on routine practice at our institution.

We acknowledge some limitations to our results. Some might argue that oxytocin use could have interfered in the results and that should have been better if oxytocin use was excluded from the study.\textsuperscript{16} We chose to maintain oxytocin in our patients because it is a common practice at our hospital and all over the world, with routine use in about 50% of women at our service. Therefore, the exclusion could have made our results less relevant in clinical practice.

On the basis of the present results, particularly the calculated number needed to harm of 4.2 (95% CI 2.6–10.2), we can suggest some caution at the beginning of combined spinal–epidural analgesia. All patients should be carefully monitored in the first one half hour after analgesia induction. Oxytocin administration in this critical period deserves attention. Indication for the technique should be evaluated in cases with previous uterine hyperactivity and possibly also in fetuses with known fetal oxygenation compromise.

Combined spinal–epidural analgesia has come to stay because of its convenience for obstetricians, anesthesiologists, and patients. Although all the medical literature is in agreement about the fact that perinatal results in those fetuses are not worsened, more investigations are needed to better understand the effects of regional analgesia on labor progress and fetal physiology.

\textbf{REFERENCES}


