Epidural analgesia in nulliparous < 4 cm vs. non-regional or epidural analgesia > 5 cm and mode of birth

Clinical question

Is the rate of cesarean section significantly different among nulliparous women who receive epidural analgesia during early labour (< 4 cm dilation) vs. those who receive non-regional or epidural analgesia > 5 cm?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Term nulliparous women in labour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Epidural analgesia &lt; 4 cm dilation</td>
</tr>
<tr>
<td>Comparison:</td>
<td>Non-regional or epidural analgesia &gt; 5 cm dilation</td>
</tr>
<tr>
<td>Primary Outcome:</td>
<td>Cesarean section</td>
</tr>
</tbody>
</table>

Search strategy

- Time period: 1990-2010
- Search terms: Epidural, regional analgesia and labour, cesarean section
- Databases searched: MEDLINE (Ovid SP); EMBASE; Cochrane CDSR, CENTRAL, DARE, & Geneva Medical Foundation
- Inclusions: meta-analysis, systematic reviews, randomized controlled trials, cohort studies
- Exclusions: studies published as abstracts (Barry, 1997; Sharma, 2003; Muir, 1996)
- Findings: titles reviewed - 289; abstracts reviewed - 220; papers reviewed - 30; papers meeting eligibility for inclusion - 23

Synthesis of the evidence

The evidence from 4 meta-analyses, 17 RCTs, and 2 cohort studies indicate that the use of epidural versus non-regional analgesia during labour or timing of
epidural analgesia during labour is not associated with significantly increased rates of cesarean section in term, nulliparous women (rate difference < 3%).

**Limitations**

1. Studies are not blinded.
2. High rates of protocol violation, drop-outs (no analgesia), and cross-over. Reported cross-over rates from non-regional to epidural analgesia ranged from 2% to 62%, and cross-over rates from epidural to non-regional ranged from 0% to 34%. Drop-out rates ranged from 0 to 35%.
3. Findings were not consistently stratified on spontaneous versus induced labour.
4. Use of high dose oxytocin protocols for induction and augmentation limit external validity to jurisdictions with low-dose protocols, such as BC.
5. Variance in management protocols for labour dystocia.
6. Time limit for second stage prior to the decision for caesarean section was less in early studies (2 hours) than what is currently accepted (4 hours).
7. 53% of RCTs were conducted in institutions where primary non-elective CS rates are lower (<10%) than current rates (BC 28%, 2008).
8. Numerous studies enrolled racial/ethnic subjects not representative of the Canadian population.
9. Epidural analgesia used in earlier studies was associated with more motor blockade due to higher doses/concentrations of anaesthetic agent.
10. Many studies administered epidural at <3.0 cervical dilatation, prior to the onset of established labour.

**Conclusions**

While the studies overwhelmingly agree that the use and/or timing of epidural analgesia during labour in nulliparous women does not appear to affect cesarean section rates, the validity of randomized controlled trials and meta-analyses is severely limited by high crossover and drop-out rates. In contrast, cohort studies undertaken “as treated” analysis with control of confounding factors demonstrate a 2-3 fold increase in cesarean section. In addition, the generalizability of included studies is limited because the majority of these studies occurred in settings where primary, non-elective cesarean section rates were <10%. A randomized controlled trial that could evaluate the impact of epidural on cesarean section would require use of analgesia in the control group that was as effective as epidural to avoid cross over, but that was not in itself associated with cesarean section.
<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Inclusion</th>
<th>Intervention/Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3,320 mixed parity</td>
<td>Early neuraxial vs. a) early parenteral opioid b) late epidural analgesia c) both early parenteral opioid and late epidural analgesia</td>
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<tr>
<td></td>
<td>N=2,980 nulliparous (All study populations nulliparous except for Ohel, 1994 which is mixed parity).</td>
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</tr>
<tr>
<td>Patient-requested neuraxial analgesia for labor: Impact on rates of caesarean and instrumental vaginal delivery</td>
<td></td>
<td><strong>Cesarean section (nulliparous)</strong>&lt;br&gt;15.3% vs. 15.3%, OR 1.0 (0.82-1.23)</td>
<td>Early neuraxial defined as epidural or combined spinal-epidural analgesia initiated ≤ 4.0 cm cervical dilation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Cesarean section (nulliparous, RCTs only)</strong>&lt;br&gt;14.5% vs. 15.2% OR 0.95 (0.72-1.24)</td>
<td>No significant heterogeneity among studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Cesarean section (individual studies, nulliparous)</strong>&lt;br&gt;Ohel ’06 17.6% vs. 18.7% OR 0.93 (0.40-2.14)&lt;br&gt;Wong 17.7% vs. 21.0% OR 0.83 (0.57-1.2)&lt;br&gt;Luxman 6.7% vs. 10.0% OR 0.64 (0.10-4.15)&lt;br&gt;Chestnut 17.6% vs. 18.7% OR 0.93 (0.40-2.14)&lt;br&gt;Chestnut 9.9% vs. 8.0% OR 1.26 (0.59-2.68)&lt;br&gt;Sharma 15.5% vs. 15.4% OR 1.0 (0.62-1.63)&lt;br&gt;Rogers 14.5% vs. 7.9% OR 1.98 (0.78-5.03)&lt;br&gt;Vahratian 17.9% vs. 17.2% OR 1.0 (0.63-1.59)</td>
<td>Oxytocin protocols: Included studies with both high and low dose protocols and studies where the dose was not reported.</td>
</tr>
</tbody>
</table>
## Meta-analysis

<table>
<thead>
<tr>
<th>Meta-analysis</th>
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<tbody>
<tr>
<td>Labour epidural for primiparous women and risk of cesarean section</td>
<td><strong>Systematic Review</strong></td>
<td><strong>Sharma, SK et al. Anesthesiology 2004; 100:142–8.</strong></td>
<td><strong>Labour analgesia and caesarean delivery. An individual patient meta-analysis of nulliparous women</strong></td>
</tr>
<tr>
<td></td>
<td>5 RCTs at Parkland Hospital, Dallas, US, 1993-2000</td>
<td><strong>Epidural vs. Intravenous meperidine</strong></td>
<td><strong>Cesarean section (5 RCTs)</strong> 10.5% vs. 10.3%, OR 1.04 (0.81-1.34)</td>
</tr>
<tr>
<td></td>
<td>N=2703 nulliparous</td>
<td><strong>Cesarean section odds ratios (individual studies)</strong></td>
<td><strong>Ramin OR 1.20 (0.73-1.97)</strong></td>
</tr>
<tr>
<td></td>
<td>Ramin, 1995, US n=693</td>
<td></td>
<td><strong>Sharma OR 1.77 (0.31-1.91)</strong></td>
</tr>
<tr>
<td></td>
<td>Sharma, 1997, US n=386</td>
<td></td>
<td><strong>Gambling OR 1.13 (0.65-1.97)</strong></td>
</tr>
<tr>
<td></td>
<td>Gambling, 1998, US n=650</td>
<td></td>
<td><strong>Lucas OR 1.05 (0.68-1.63)</strong></td>
</tr>
<tr>
<td></td>
<td>Sharma, 2002, US n=459</td>
<td></td>
<td><strong>Sharma OR 0.81 (0.41-1.61)</strong></td>
</tr>
<tr>
<td></td>
<td>Inclusion:</td>
<td></td>
<td><strong>Epidural: Initiated with bupivacaine or intrathecal sufentanil and maintained with low dose (0.0625% or 0.125%) bupivacaine with fentanyl</strong></td>
</tr>
<tr>
<td></td>
<td>• healthy term nulliparous (n=2188)</td>
<td></td>
<td><strong>Intravenous opioid: Initiated with 50 mg meperidine and 25 mg promethazine hydrochloride and maintained with intravenous boluses of meperidine as needed.</strong></td>
</tr>
<tr>
<td></td>
<td>• pregnancy induced hypertension (n= 515)</td>
<td></td>
<td><strong>No significant heterogeneity among studies.</strong></td>
</tr>
<tr>
<td></td>
<td>• spontaneous labour</td>
<td></td>
<td><strong>For all trials combined:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Oxytocin protocols:</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
<td><strong>Not provided. 48% of epidural group and 40% intravenous meperidine group received oxytocin.</strong></td>
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<td></td>
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<td></td>
<td><strong>Epidural group:</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
<td><strong>No analgesia: 14.1% Cross-over: 3.7%</strong></td>
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<td><strong>IV meperidine group:</strong></td>
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<td></td>
<td></td>
<td></td>
<td><strong>No analgesia: 11.8% Cross-over: 13.6%</strong></td>
</tr>
</tbody>
</table>
### Rates of caesarean section and instrumental vaginal delivery in nulliparous women after low concentration epidural infusions or opioid analgesia: Systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>N (nulliparous)</th>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu E. et al. BMJ 2004; 328:1410–20</td>
<td>N=2962</td>
<td>RCTs comparing low concentration bupivacaine (≤ 0.125%) with parenteral opioids, term, uncomplicated pregnancies, cephalic presentation, spontaneous and induced labour</td>
</tr>
</tbody>
</table>

#### Epidural vs. parenteral opioids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cesarean section</strong></td>
<td>12.1% vs. 11.3% OR 1.03 (0.71-1.48)</td>
<td>Heterogeneity attributed to Thorpe. When excluded from sensitivity analysis, there is no heterogeneity.</td>
</tr>
<tr>
<td><strong>Cesarean section (excluding Thorpe)</strong></td>
<td>11.7% vs. 11.6% OR 1.01 (0.80-1.28)</td>
<td>Included studies with both high dose and low dose oxytocin protocols.</td>
</tr>
<tr>
<td><strong>Cesarean section (individual studies)</strong></td>
<td>Dickinson: 17.2% vs. 14.2% OR 1.26 (0.89-1.77)</td>
<td>Crossover rates among included studies ranged from 0 – 27.7% in the epidural group and 1.4 - 62.1% in the opioid group.</td>
</tr>
<tr>
<td></td>
<td>Sharma '02: 7.1% vs. 8.6% OR 0.81 (0.41-1.61)</td>
<td></td>
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<tr>
<td></td>
<td>Loughnan: 11.8% vs. 12.9% OR 0.91 (0.56-1.47)</td>
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<td></td>
<td>Clarke: 9.6% vs. 13.6% OR 0.68 (0.34-1.36)</td>
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<td></td>
<td>Bofill: 10.2% vs. 5.9% OR 1.82 (0.41-8.06)</td>
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<tr>
<td></td>
<td>Sharma '97: 4.6% vs. 5.8% OR 0.78 (0.31-1.91)</td>
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<tr>
<td></td>
<td>Thorpe: 25% vs. 2.2% OR 14.67 (1.82-118.22)</td>
<td></td>
</tr>
</tbody>
</table>
**Labour epidural for primiparous women and risk of cesarean section**

**Systematic Review**

<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>Inclusion</th>
<th>Intervention/Findings</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Halpern S. et al.  
JAMA;1998;280 (24)  
2105-09.  
**Effect of Epidural vs Parenteral Opioid Analgesia on the Progress of Labor: A Meta-analysis**  
10 RCTs, 1980-1997  
N=2369 mixed parity  
nulliparous n = 1614  
multiparous n = 755  
7/10 RCTs nulliparous women  
Sharma, 1997, US n=386  
Bofill, 1997, US n=100  
Nikkola, 1997, Finland n=20  
Barry, 1997, US n=318  
Muir, 1996, Canada n=50  
Ramin, 1995, US n=485  
Robinson, 1980, UK n=80  
Inclusion:  
• spontaneous and induced labour  
healthy women with  
uncomplicated pregnancies  
Epidural vs. parenteral opioid  
Cesarean section (n=1025 nulliparous)  
8.5% vs. 7.7%, OR 1.28 (0.55-2.93)  
Cesarean section (individual studies)  
Sharma 3.6% vs. 4.5%  
OR 0.80 (0.38-1.70)  
Bofill 10.2% vs. 5.9%  
OR 1.82 (0.41-8.06)  
Barry 9.6% vs. 13.6%  
OR 0.68 (0.34-1.36)  
Muir 10.7% vs. 9.1%  
OR 1.20 (0.18-7.89)  
Ramin 9.0% vs. 3.9%  
OR 2.45 (1.36-4.41)  
Robinson CS not an outcome  
Nikkola CS not an outcome  
Heterogeneity attributed to Thorpe.  
Sensitivity analysis not provided.  
7/10 studies reported outcomes by intention-to-treat; 2 reported both intention-to-treat and protocol compliant, and one reported only protocol compliant.  
2 studies included where CS not an outcome.  
Oxytocin protocols:  
Not provided. 9 studies enrolled women in spontaneous labour and one study included inductions.  
7/10 studies included only nulliparous women.  
Crossover rates ranged from 2.2% - 3.2% in the epidural group and 2.2% - 51.8% in the opioid group.  
Drop-out (no analgesia) rates ranged from 2% - 34.9% in the epidural group and 26.1% (one study reporting) in the opioid group. |
**Labour epidural for primiparous women and risk of cesarean section**

**Systematic Review**


**Epidural analgesia in the latent phase of labor and the risk of caesarean delivery. A five-year randomized controlled trial.**

- **Inclusion:**
  - nulliparous
  - spontaneous labour
  - term
  - vertex presentation
  - > 1.0 cm dilation

- **Exclusion:**
  - allergy to opioids
  - history of centrally-acting drugs
  - alcohol or opioid dependency
  - chronic pain
  - psychiatric disease history
  - < 18 or > 45 years
  - non-vertex presentation
  - induction of labour
  - diabetes mellitus
  - hypertensive disorders of pregnancy
  - twin gestation

**China**

- N = 12,793
- Latent phase n = 6,394
- Active phase n = 6,399

**Latent phase epidural ≥ 1.0 cm. vs. active labour epidural ≥ 4 cm.**

**Cesarean section**

23.2% vs. 22.8% p = .51

**Epidural protocol:**

- Epidural analgesic mixture of 0.125% (1.25 mg/ml) ropivacaine plus 0.3 ug/ml sufentanil as single dose, followed by patient-controlled infusion with a 10-ml bolus without background infusion.

- Repeatable meperidine (25 mg IM) was rescue analgesic in active labour epidural group.

- Median cervical dilation at epidural placement: 1.6 cm in early group vs. 5.1 cm in delayed group P = < 0.0001.

- Oxytocin protocol:
  - Not provided.

- Crossover: 1.5% of women in active labour assigned to the latent phase group and 0.7% of women assigned to active phase were in latent phase labour when epidural received.

- Did not compare epidural with other analgesia.
### Systematic Review: Labour Epidural for Primiparous Women and Risk of Cesarean Section

#### Early vs. Late Initiation of Epidural Analgesia in Labour: Does it Increase the Risk of Cesarean?

<table>
<thead>
<tr>
<th>Israel</th>
<th>Early Epidural &lt; 3 cm (mean 2.4 cm) vs. Delayed Epidural ≥ 4 cm (mean 4.6 cm)</th>
<th>Enrolled at First Request for Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 449&lt;br&gt;Immediate epidural &lt; 3 cm n = 221&lt;br&gt;Delayed epidural ≥ 4 cm n = 228</td>
<td>Early Group – Epidurals were Started Immediately. In Delayed Group, IV Pethidine and Promethazine Provided, Until Epidural Placement.</td>
</tr>
<tr>
<td></td>
<td>Inclusion:&lt;br&gt;• nulliparous&lt;br&gt;• spontaneous or induced labour&lt;br&gt;• ≥ 36 weeks&lt;br&gt;• ≥ 2 painful contractions in 10 min.&lt;br&gt;• Cx ≤ 3 cm dilated and 80% effaced</td>
<td>Immediate Epidural: Mean Cervical Dilation 2.4 cm&lt;br&gt;Delayed Epidural: Mean Cervical Dilation 4.6 cm</td>
</tr>
<tr>
<td></td>
<td>Exclusion:&lt;br&gt;• contraindication to epidural&lt;br&gt;• cervical dilation &gt; 3 cm at time of enrollment&lt;br&gt;• estimated fetal weight &gt; 4000 g.&lt;br&gt;• medical complications of pregnancy&lt;br&gt;• abnormal admission fetal heart tracing</td>
<td>Epidural Bolus of 10 ml Ropivacaine 0.2% and 50 μg Fentanyl. Epidural Maintained with Continuous Infusion of Ropivacaine 0.1% with Fentanyl 0.0002% at 10 ml/hr. Further Bolus of Ropivacaine 0.2% 5-10 ml Provided Upon Request.</td>
</tr>
<tr>
<td></td>
<td>Cesarean Section&lt;br&gt;13% vs. 11% p = .77</td>
<td>Early Epidural: 4.5% Did Not Receive Epidural. 47% Received Pethidine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed Epidural Group: 13.6% Did Not Receive an Epidural. 80% Received Pethidine.</td>
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<tr>
<td></td>
<td></td>
<td>Epidural Not Compared with Other Analgesia.</td>
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<tr>
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<td>Oxytocin Protocol: Not Provided. Oxytocin Use 36% in Early Group vs. 37% in Late Group.</td>
</tr>
</tbody>
</table>
### Randomized controlled trials

<table>
<thead>
<tr>
<th>Inclusion</th>
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</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Early (˂ 4 cm) Intrathecal vs. late (˃ 4 cm) systemic (IV &amp; IM) hydromorphone</td>
<td>Systemic-analgesia: At first request for analgesia – 25 ug fentanyl intrathecally (early group) vs. hydromorphone 1 mg IM and 1 mg IV (late group).</td>
</tr>
<tr>
<td>N=728</td>
<td>Cesarean section 17.8% vs. 20.7% Risk difference: -2.9% (95%CI -9.0 – 3.0) p = .31</td>
<td>At second request Early group: if the cervix &lt; 4.0 cm dilated, a 15-ml epidural bolus of bupivacaine (0.625 mg per milliliter) with fentanyl (2 μg per milliliter) was given, and if the cervix ˃ 4.0 cm dilated, a 15-ml epidural bolus of bupivacaine (1.25 mg per milliliter) was given. Both groups had patient controlled epidural analgesia. Late group: hydromorphone repeated if cervix &lt; 4cm otherwise, patient controlled epidural analgesia was initiated. Epidural analgesia was given at the third analgesia request, regardless of cervical dilatation. Drop out (no analgesia) and crossover rates not given. Oxytocin protocol: Not provided. Oxytocin use &gt; 92% in both trial arms.</td>
</tr>
<tr>
<td>Early intrathecal analgesia n = 366</td>
<td></td>
<td></td>
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<tr>
<td>Late systemic analgesia n = 362</td>
<td></td>
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</tr>
<tr>
<td>Inclusion:</td>
<td>Early (&lt; 4 cm) Intrathecal vs. late (&gt; 4 cm) systemic (IV &amp; IM) hydromorphone</td>
<td></td>
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<tr>
<td>- healthy, low risk women</td>
<td>Cesarean section 17.8% vs. 20.7% Risk difference: -2.9% (95%CI -9.0 – 3.0) p = .31</td>
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<tr>
<td>- term (37– 42 weeks)</td>
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<tr>
<td>- nulliparous</td>
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<td></td>
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<tr>
<td>- spontaneous labour or spontaneous rupture of membranes</td>
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<tr>
<td>- cervical dilation &lt;4 cm</td>
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</tr>
<tr>
<td>Exclusion:</td>
<td>Early (&lt; 4 cm) Intrathecal vs. late (&gt; 4 cm) systemic (IV &amp; IM) hydromorphone</td>
<td></td>
</tr>
<tr>
<td>- non-vertex presentation</td>
<td>Cesarean section 17.8% vs. 20.7% Risk difference: -2.9% (95%CI -9.0 – 3.0) p = .31</td>
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<tr>
<td>- scheduled induction of labour</td>
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<tr>
<td>- contraindication to opioid analgesia</td>
<td>Cesarean section 17.8% vs. 20.7% Risk difference: -2.9% (95%CI -9.0 – 3.0) p = .31</td>
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**Labour epidural for primiparous women and risk of cesarean section**

**Systematic Review**

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<tr>
<td></td>
<td></td>
<td>Cesarean Section</td>
<td>PCEA: 3-5 ml aliquots 0.1% bupivacaine, then maximum 25 mL with 100 μg fentanyl; followed by PCEA pump 0.08% bupivacaine with fentanyl 1.6 μg/mL q 10 min. prn.</td>
</tr>
<tr>
<td></td>
<td>Canada N=242 PCIA n = 118 PCEA n = 124</td>
<td></td>
<td>Oxytocin protocol: Not provided. 52% PCIA group and 44% PCEA group received oxytocin. CS performed for dystocia after giving a trial of oxytocin therapy of at least 2 h.</td>
</tr>
<tr>
<td></td>
<td>Inclusion: • healthy, low risk women • term (37–42 weeks) • nulliparous • spontaneous labour</td>
<td></td>
<td>PCIA group: 51/118 (43%) requested epidural – actual proportion who received it not clearly stated; 36% received analgesia before randomization.</td>
</tr>
<tr>
<td></td>
<td>Exclusion: • preeclampsia • antenatal hemorrhage • BMI &gt;35 • multiple gestation • malpresentation • known fetal anomalies • fetal distress</td>
<td></td>
<td>PCEA group: no crossover; 44% received analgesia before randomization.</td>
</tr>
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</table>
### Randomized controlled trials

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</thead>
<tbody>
<tr>
<td>Australia</td>
<td>N = 992 Epidural n = 493 CMS n = 499</td>
<td>Epidural vs. continuous midwifery support (CMS) and attempt to avoid epidural Cesarean Section 17.2% vs. 14.2% p = 0.22</td>
<td>Epidural analgesia: combined spinal-epidural technique, with patient-controlled epidural analgesia. Continuous midwifery support: 1:1 midwife-patient ratio throughout labour, intramuscular pethidine (1.5 mg/kg maternal body weight), nitrous oxide inhalation or non-pharmacological methods of pain relief. Oxytocin protocol: 2 mU/min if cervix dilation &lt;1 cm/h, increased by 2 mU/min at 30 minute intervals to maximum 36 mU/min. 45% CMS group and 46% epidural group induced. Crossover rates: Epidural to CMS: 27.8% CMS to epidural: 61.3%</td>
</tr>
</tbody>
</table>

| Sharma. SK., Anesthesiology 2002;96(3):546–51 Cesarean delivery: a randomized trial of epidural analgesia versus intravenous meperidine analgesia during labor in nulliparous women. | United States | Epidural vs. IV meperidine Cesarean Section 7% vs. 9% p =0.61 | Epidural: initiated with 0.25% bupivacaine and maintained with 0.0625% bupivacaine and fentanyl 2 g/ml at 6 ml/h with 5-ml bolus doses every 15 min prn using a patient-controlled pump. IV meperidine: 50 mg meperidine with 25 mg promethazine hydrochloride as an initial bolus, followed by 15 mg meperidine every 10 min prn, using a patient-controlled pump. cont. |
## Labour epidural for primiparous women and risk of cesarean section

### Systematic Review

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<th>Intervention/Findings</th>
<th>Comments</th>
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</thead>
</table>
| Sharma. SK., Anesthesiology 2002;96(3):546–51 cont. | United Kingdom  
N = 369 nulliparous  
Epidural n = 184  
Non-epidural n = 185  
Inclusion:  
• primigravida women  
• term  
• spontaneous labour  
• normal obstetric and medical history | Epidural vs. non-epidural Cesarean Section  
7% vs. 9% p = > .05 | Oxytocin protocol:  
6 mU/min if cervix dilation <1 cm/h, increased by 6 mU/min every 40 minutes up to 42 mU/min. 45% epidural group and 34% IV meperidine group received oxytocin.  
IV meperidine:  
Cross-over to epidural: 6%  
Refusal of allocated analgesia and received other analgesia: 10%  
Epidural: refused epidural and had a different (unspecified) analgesic: 5.3% |

A randomised controlled trial of epidural compared with non-epidural analgesia in labour. | | | |
<table>
<thead>
<tr>
<th>Randomized controlled trials</th>
<th>Inclusion</th>
<th>Intervention/Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loughnan B. et al. British Journal of Anaesthesia 2000;84(6) 715-9.</td>
<td>United Kingdom N= 614 IM pethidine n= 310 Epidural bupivacaine n=304 Inclusion: • healthy, low risk, nulliparous • term • cephalic presentation Exclusion: • women with any risk factors determining method of analgesia during labour</td>
<td>Epidural vs. IV meperidine Cesarean Section 12.0% vs.13.0% p = .7</td>
<td>Oxtytocin protocol: 4 mU/min, increased every 15 minutes up to maximum of 40 mU/min if cervix dilation &lt;1 cm/h. 61% of epidural group and 57% of IV meperidine group received oxytocin. Cross over: Epidural group: 18.7% IV meperidine group: 57% Drop out: Epidural: (no epidural or pethidine): 1% Pethidine: 1%</td>
</tr>
<tr>
<td>Gambling, D R. et al. Anesthesiology. 1998;89(6):1336-44.</td>
<td>United States N = 644 nulliparous CSE nulliparous n = 330 IV meperidine nulliparous n = 314 Inclusion: • singleton fetus • mixed parity • 3-5 cm dilation and regular contractions • healthy women • spontaneous labour</td>
<td>Combined spinal-epidural (CSE) vs. IV meperidine Cesarean Section (nulliparous alone) 10.0% vs. 9.0%, p = &gt; .05 Cesarean Section (nulliparous alone, as treated) 11.0% vs. 5%, p = &lt; .023</td>
<td>CSE: 10 ug intrathecal sufentanil, then epidural bupivacaine and fentanyl at their next request for analgesia. IV meperidine: 50 mg on demand to a maximum of 200 mg in 4 h. Cross over: CSE: 13.3% IV meperidine: 26.1% Dropout:(no analgesia) CSE: 8.4% IV meperidine:6.9% An additional 6.9% in the CSE group and 4.9% in the meperidine group were noted to have had rapid deliveries but the analgesia used, if any, is not stated.</td>
</tr>
</tbody>
</table>
### Labour epidural for primiparous women and risk of cesarean section

#### Systematic Review

<table>
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<tr>
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</table>
N = 318  
Epidural analgesia n = 156  
Intravenous opioid n = 162  
Inclusion:  
- nulliparous  
- ≥ 36 weeks  
- cephalic presentation  
- spontaneous labour (≥ 50% effacement, ROM and painful contractions ≥ 2 q 15 min)  
Exclusion:  
- medical conditions precluding epidural  
- multiple gestation  
- maternal or fetal conditions precluding trial of labour | **Epidural vs. Intravenous opioid**  
**Cesarean Section**  
9.6% vs.13.6%, RR 0.71 (0.38-1.31)  
**Cesarean Section (as treated)**  
7.7% vs. 8.8%, RR 1.15 (0.45-2.91) | Epidural: 9 ml 0.25% bupivacaine with 50 ug fentanyl in 3 doses over 10 min interval, followed by continuous infusion 0.125% bupivacaine with 50 ug fentanyl at 12 ml/hour.  
IV Opioid: meperidine 50-75 mg q 90 mins. prn  
Oxytocin protocol:  
6 mU/min and increased by 6 mU every 15 minutes until there were 7 contractions every 15 minutes. 75% of epidural group and 72% IV opioid group received oxytocin.  
Cross over:  
Dropout:  
Epidural: 34%  
IV Opioid: 52%  
IV Opioid: not stated |
N = 60  
Early epidural < 4 cm n = 30  
Late epidural ≥ 4 cm n = 30  
Inclusion:  
- nulliparous  
- term  
- cephalic presentation  
- spontaneous labour | **Early epidural < 4 cm vs. Late epidural ≥ 4 cm**  
**Cesarean Section**  
6.6% vs.10.0% p = > .05 | Lumbar epidural 8.0 ml 0.25% bupivacaine with top-ups until full dilation.  
Mean cx dilation early group: 2.3 cm  
Mean cx dilation in late group: 4.5 cm  
Late group did not receive any analgesia prior to epidural.  
Oxytocin protocol:  
2 mU every 30 min  
53% of early group and 60% of late group received oxytocin. |
## Labour epidural for primiparous women and risk of cesarean section

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#### Randomized controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
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</tr>
</thead>
</table>
Epidural nulliparous n =197  
PCIA nulliparous n = 189 | Epidural vs. Meperidine PCIA (patient controlled intravenous analgesia)  
Cesarean Section 5% vs. 6% p = > .05  
Cesarean Section (as treated) 5% vs. 7% p = > .05 | Randomized at 3-5 cm cervical dilation  
Epidural: maintained with continuous epidural infusion of 0.125% bupivacaaine with 2 micro gram/ml fentanyl.  
PCIA: maintained with 10-15 mg meperidine given every 10 min prn  
Oxytocin protocol: 6 mU/min, ans increased by 6 mU/min at 40-min intervals, to a max 42 mU/min.  
Cross-over:  
Dropout: Epidural: 2.2%  
PCIA: 1.4% |
Epidural n = 49  
Narcotic n = 51 | Epidural vs. Narcotic  
Cesarean section for dystocia 8% vs. 6% p = > .05 | Epidural Group: Three to five ml boluses of 0.25% bupivacaaine, with or without 50 to 100 I ug fentanyl, flowed by continuous infusion of 0.125% bupivacaaine with 1.5 ug/ml fentanyl titrated to maintain level of analgesia.  
Narcotic group: women received 1 to 2 mg intravenous doses of butorphanol q 1 to 2 hours, prn.  
Oxytocin protocol: 6 mU/min, increased by 6 mU every 30 minutes up to maximum 42 mU/min if cervical dilation < 1 cm/h. |

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### Insufficient power to evaluate outcomes.
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</table>
| **Bofill JA. Et al.**  
American Journal of Obstetrics and Gynecology 1997;177:1465–70. cont. | • women who received cervical ripening agents | | Crossover:  
Epidural: 0  
Narcotic: 23.5%  
Dropout: 4.0%  
Narcotic group: 0  
Oxytocin augmentation: 69% in the epidural group and 82.3% in the narcotic group.  
Insufficient power to evaluate outcomes. |
| **Ramin SM.**  
**Randomized trial of epidural versus intravenous analgesia during labor.** | United States  
N=1330 combined parity  
n = 673 nulliparous  
Epidural n= 338  
IV analgesia n= 335  
Inclusion:  
• healthy, term pregnancies  
• mixed parity  
• spontaneous labour  
• 3-5 cm dilated  
Exclusion:  
• pregnancy complications  
**Epidural vs. IV analgesia**  
**Cesarean section (nulliparous “as treated”)**  
Risk ratio: 2.55 (95% CI 1.5-4.3)  
For combined parity:  
Epidural group: protocol violations 35%  
IV analgesia group: protocol violations 55%  
Oxytocin protocol:  
6 mU/min, increased by 6 mU every 40 minutes up to maximum 42 mU/min. 32% of epidural group and 23% of IV analgesia group received oxytocin.  
Intention to treat reports only as operative deliveries for combined parity.  
Cross-over: Dropout:  
Epidural: 0  
Epidural: 35%  
Meperidine: 15.4%  
Meperidine 18.9% |
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</table>
N = 150  
Early n = 74  
Late n = 75 | Early (3-<5 cm) vs. late (≥ 5 cm) epidural analgesia  
Cesarean Section  
18% vs. 19% RR 0.94 (0.48-1.84) | Early group: 3 ml 1.5% lidocaine with epinephrine, and after 10 minutes 5 ml 0.25% bupivacaine, then boluses prn. At 5 cm dilation, continuous infusion of 0.125% bupivacaine at 12 ml/hour. Late group: nalbuphine 10 mg IV if < 5 cm; then epidural protocol as per early group once ≥ 5 cm.  
Oxytocin protocol: Oxytocin augmentation (1 mU every 30 min) until an adequate labor pattern. |
N = 334  
Early n = 172  
Late n = 162 | Early (3-<5 cm) vs. late (≥ 5 cm) epidural analgesia  
Cesarean Section  
10% vs. 8% RR 1.22 (0.62-2.4) | Early group: 3 ml 1.5% lidocaine with epinephrine, and after 10 minutes 5 ml 0.25% bupivacaine, then boluses prn. At 5 cm dilation, continuous infusion of 0.125% bupivacaine at 12 ml/hour. Late group: nalbuphine 10 mg IV if < 5 cm; then epidural protocol as per early group once ≥ 5 cm.  
Oxytocin protocol: Dose not reported. 31% of early group and 38% of late group required oxytocin.  
Results not analyzed for 5 subjects in the late group who received early epidural |
Labour epidural for primiparous women and risk of cesarean section

Systematic Review

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<tbody>
<tr>
<td>Chestnut, D. et al. Anesthesiology 1994; 80; 1201-8. Cont.</td>
<td>• insulin dependent diabetes • estimate fetal weight ≥ 4500 g</td>
<td></td>
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</tr>
<tr>
<td>Thorp, et al. AJOG. 1993;169:851-8.</td>
<td>United States N = 93 Narcotic analgesia n = 45 Epidural analgesia n = 48</td>
<td>Narcotic vs. Epidural Cesarean section 25% vs. 2.2% p = &lt; .05</td>
<td>Narcotic: 75 mg meperidine and 25 mg promethazine hydrochloride IV q 90 min. prn Epifural: continuous infusion 0.125% bupivacaine, into 2nd stage Oxytocin protocol: 1 mU/min, increased by 1 mU/min every 30-45 minutes. Crossover rates: Epidural: 0 Narcotic: 2.1% Dropout: Epidural: 2.2% Narcotic: 0 7 CS occurred in second stage. Mean second stage 115 min.</td>
</tr>
<tr>
<td>The effect of intrapartum epidural analgesia on nulliparous labor: a randomized, controlled, prospective trial.</td>
<td>Inclusion: • healthy nulliparous • singleton fetus • spontaneous labour</td>
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</table>

**Prospective**

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<thead>
<tr>
<th>Inclusion</th>
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<tr>
<th>Cohort Study</th>
<th>Inclusion</th>
<th>Intervention/Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uyen-Sa, t. Maternal Child Health: 2009;September 18.</td>
<td>San Diego, 1994-1996 N=2052 Inclusion: combined parity • women at low risk for medical complications Exclusion: • multiple births • private or military insurance • first prenatal visit &gt; 32 weeks • any medical condition that would require emergency or preclude epidural placement • induction with oxytocin and/or prostaglandin and/or ARM • preterm &lt; 37 weeks • birth weight ≥4500 grams • no previous cesarean delivery</td>
<td>Epidural vs. no regional analgesia Cesarean section (nulliparous) 17.6% vs. 4.6% Unadjusted RR 3.8 (2.4-6.0) *Adjusted RR 2.4 (1.5-3.7) * Adjusted for model of care, cervical dilation at admission &lt; 4 cm, major antepartum complications, any complications at presentation, birth weight, gestational age at birth, infant’s sex, maternal age, height, weight, education, marital status, maternal race, language spoken, station, maternal country of origin, and maternal narcotics use.</td>
<td>Epidural management in 1994-1996 may have been different than that offered today. Oxytocin protocol: Not provided.</td>
</tr>
<tr>
<td>Lieberman E. 1996. Obstetrics and Gynecology: 88(6).</td>
<td>USA, 1991 - 1993 N=1733 Inclusion: • low-risk • term • singleton vertex presentation • spontaneous labour • no medical contraindications to</td>
<td>Epidural vs. non-regional analgesia Cesarean section (nulliparous) 17.0% vs. 4.0% *Adjusted RR 3.7 (2.4-5.7) * Adjusted for maternal age, race, insurance (private, public, other), pre-pregnant weight, height, infant</td>
<td>Epidural – 0.25% bupivacaine (12-16 ml) via the L2-3 or L3-4 at &lt; 8 cm dilation, followed by continuous infusion of 0.125% bupivacaine plus 2 μg/mL fentanyl. Oxytocin protocol: Not stated. 27% of epidural group and 34% of non-regional analgesia group received oxytocin.</td>
</tr>
</tbody>
</table>
### Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Intervention/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• epidural analgesia</td>
<td>birth weight, gestational age, infant sex, dilation at admission, initial rate of cervical dilation, station of the fetal head at admission, active management of labour protocol, ruptured membranes on admission, maternal chronic hypertension, and pregnancy-induced hypertension.</td>
</tr>
<tr>
<td>• at least one hour of first stage of labour after admission</td>
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</tbody>
</table>

Epidural analgesia in nulliparous < 4 cm vs. non-regional or epidural analgesia > 5 cm and mode of birth

Clinical question

Is the rate of cesarean section significantly different among nulliparous women who receive epidural analgesia during early labour (< 4 cm dilation) vs. those who receive non-regional or epidural analgesia > 5 cm?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Term nulliparous women in labour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Epidural analgesia ≤ 4 cm dilation</td>
</tr>
<tr>
<td>Comparison:</td>
<td>Non-regional or epidural analgesia &gt; 5 cm dilation</td>
</tr>
<tr>
<td>Primary Outcome:</td>
<td>Cesarean section</td>
</tr>
</tbody>
</table>

Search strategy

- Time period: 1990-2010
- Search terms: Epidural, regional analgesia and labour, cesarean section
- Databases searched: MEDLINE (Ovid SP); EMBASE; Cochrane CDSR, CENTRAL, DARE, & Geneva Medical Foundation
- Inclusions: meta-analysis, systematic reviews, randomized controlled trials, cohort studies
- Exclusions: studies published as abstracts (Barry, 1997; Sharma, 2003; Muir, 1996)
- Findings: titles reviewed - 289; abstracts reviewed - 220; papers reviewed - 30; papers meeting eligibility for inclusion - 23

Synthesis of the evidence

The evidence from 4 meta-analyses, 17 RCTs, and 2 cohort studies indicate that the use of epidural versus non-regional analgesia during labour or timing of...
Epidural vs. non-regional analgesia in nulliparous women and mode of birth
Systematic Review

epidural analgesia during labour is not associated with significantly increased rates of cesarean section in term, nulliparous women (rate difference < 3%).

Limitations

1. Studies are not blinded.
2. High rates of protocol violation, drop-outs (no analgesia), and cross-over. Reported cross-over rates from non-regional to epidural analgesia ranged from 2% to 62%, and cross-over rates from epidural to non-regional ranged from 0% to 34%. Drop-out rates ranged from 0 to 35%.
3. Findings were not consistently stratified on spontaneous versus induced labour.
4. Use of high dose oxytocin protocols for induction and augmentation limit external validity to jurisdictions with low-dose protocols, such as BC.
5. Variance in management protocols for labour dystocia.
6. Time limit for second stage prior to the decision for caesarean section was less in early studies (2 hours) than what is currently accepted (4 hours).
7. 53% of RCTs were conducted in institutions where primary non-elective CS rates are lower (<10%) than current rates (BC 28%, 2008).
8. Numerous studies enrolled racial/ethnic subjects not representative of the Canadian population.
9. Epidural analgesia used in earlier studies was associated with more motor blockade due to higher doses/concentrations of anaesthetic agent.
10. Many studies administered epidural at <3.0 cervical dilatation, prior to the onset of established labour.

Conclusions

While the studies overwhelmingly agree that the use and/or timing of epidural analgesia during labour in nulliparous women does not appear to affect cesarean section rates, the validity of randomized controlled trials and meta-analyses is severely limited by high crossover and drop-out rates. In contrast, cohort studies undertaken “as treated” analysis with control of confounding factors demonstrate a 2-3 fold increase in cesarean section. In addition, the generalizability of included studies is limited because the majority of these studies occurred in settings where primary, non-elective cesarean section rates were <10%. A randomized controlled trial that could evaluate the impact of epidural on cesarean section would require use of analgesia in the control group that was as effective as epidural to avoid cross over, but that was not in itself associated with cesarean section.