# $M \mbox{edical}$ Risks of Epidural Anesthesia During Childbirth

By Lewis Mehl-Madrona, M.D., Ph.D. and Morgaine Mehl-Madrona

#### The Medical Risks of Epidural Anesthesia

# Quick Index to this Paper

- Introduction
- Epidurals and pain relief
- Overall complication rates for epidural anesthesia
  - O Effects of epidurals on cesarian rate
  - O Significant low blood pressure (hypotension)
  - o <u>Fetal distress</u>
  - o <u>IV cannulation</u>
  - o <u>Trauma to blood vessels</u>
  - o <u>Punctured dura</u>
  - O <u>Infection</u>
  - O <u>Backache</u>
  - O Broken catheters
  - O <u>Abnormal uterine contractions</u>
  - O Second stage labor effects
  - o Inadequate pain relief
  - O Accidental spinal anesthesia
  - O Maternal heart attack or spinal cord ischemia
  - O <u>Asthmatics</u>
  - O <u>Medication interactions</u>
  - o Interactions with other illnesses
  - O <u>Malignant hyperthermia</u>
  - o <u>Respiratory arrest</u>
  - O Other neurological disabilities
  - O Nausea and vomiting

- o <u>Allergic conditions</u>
- O <u>Heart problems</u>
- O <u>Headache</u>
- o Motor blockade
- O Use in VBAC (Vaginal Birth After Cesarian)
- O <u>Technical considerations</u>
- O <u>Herpes simplex</u>
- <u>Case examples: mild problems</u>
- Permanent disability from epidural anesthesia
- Deaths from epidural anesthenia
- <u>Critique of 3 other studies</u>
  - O Does epidural analgesia protect against cesarian section in nulliparous patients?
  - O Epidural anesthesia and uterine function
  - O The relationship of ambulation in labor to operative delivery
- References
  - Related Childbirth Risk Resources

**E** pidural anesthesia has become increasingly popular for childbirth. The popular book, <u>*What to Expect when You're Expecting,*</u> for example, portrays epidurals as perfectly safe. The risks, however, may be greatly underplayed.

#### **Epidurals and pain relief**

For the most part, epidural analgesia does effectively relieve labor pain.<sup>1</sup> Obstetrical anesthesiologists continue to state that epidural analgesia has other, potentially catastrophic, adverse effects but, with safe clinical practice, these problems are extremely rare. We will suggest in the material that follows that these complications are not extremely rare, and that women are not receiving adequate informed consent about what these complications are and their accompanying frequency. Nor are they being offered any serious alternatives to epidural anesthesia. Despite this, anesthesiologists such as Eberle and Norris argue that specific anaesthetic techniques ... or obstetrical management can limit or eliminate these risks of epidural labour analgesia. What must be remembered for any technical procedure, is that it is studied in major academic centers where highly skilled professors supervise residents and all outcomes are monitored closely. The actual practice, however, takes place in smaller institutions by less qualified individuals so that the actual complication rates of any procedure (obstetric, cardiac, pulmonary) are always higher than what are found in studies.

#### Overall complications rates for epidural anesthesia

A general estimate of the overall complication rate of epidural anesthesia is 23%.<sup>2</sup>

# 1. Effects of epidurals on cesarean rate:

When the dose is too large or when it sinks down into the sacral ("tailbone") region of the body, the perineum and the vagina are anesthetized. Anesthetic is intentionally injected into this area late in labor to deaden all sensation. When it "accidentally" happens earlier in labor, the muscles of the pelvic floor are prematurely relaxed, thereby interfering with the normal flexion and rotation of the baby's head as it passes through the birth canal. This interference can lead to abnormal presentations which are more dangerous for the baby or to what is called "failure to descend," an indication for Cesarean birth.

Thorp, et al<sup>3</sup> studied 711 consecutive nulliparous women at term, with cephalic fetal presentations and spontaneous onset of labor. They compared 447 patients who received epidural analgesia in labor with 264 patients who received either narcotics or no analgesia.

The incidence of cesarean section for dystocia was significantly greater (p < 0.005) in the epidural group (10.3%) than in the nonepidural group (3.8%). There remained a significantly increased incidence (p < 0.005) of cesarean section for dystocia in the epidural group after selection bias was corrected and the following confounding variables were controlled by multivariate analysis: maternal age, race, gestational age, cervical dilatation on admission, use of oxytocin, duration of oxytocin use, maximum infusion rate of oxytocin, duration of labor, presence of meconium, and birth weight.

The incidence of cesarean section for fetal distress was similar (p > 0.20) in both groups. There were no clinically significant differences in frequency of low Apgar scores at 5 minutes or cord arterial and venous blood gas parameters between the two groups. They concluded that epidural analgesia in labor increases the incidence of cesarean section for dystocia in nulliparous women.

Frequently the epidural is so effective that it eliminates uterine contractions. The nerves which tell the uterus to contract are all anesthetized. The uterus becomes quiet and must be driven artifically with the hormone oxytocin (Pitocin or Syntocinon).

As the cervix becomes fully dilated and the head descends, the woman (in a normal birth) feels pain and pressure in the lower pelvis and rectum. The last injection of anesthetic during the process of epidural anesthesia occurs after the head has rotated and come down onto the perineum. Higher concentrations of anesthetic are used to assure perineal relaxation. Sometimes the mother is sat upright or at least at a 45 degree angle to be certain that the anesthetic will descend to the sacral nerve roots. When the sacral nerve roots are blocked, the woman looses the urge to push.

After controlling for potentially confounding variables with multiple logistic regression analysis, Adashek, et al<sup>4</sup> found that epidural anesthesia was an independent risk factor for cesarean birth among women over age 35 (R = 0.195, p < 0.001).

At the 1997 meeting of the American Society for Anesthesiology, a press release was issued about four studies involving a combined total of more than 22,000 women claiming that labor epidural analgesia does not increase a woman's risk of having a cesarean delivery.<sup>5</sup> Three of the studies were presented at the annual meeting of the American Society of Anesthesiologists. The fourth appeared in the September 1997 issue of the medical journal of Anesthesiology.

"The findings have significant implications for physicians, patients and insureres," said one of the reserchers, Steven T. Fogel, M.D., an anesthesiologist at Washington University School of Medicine in St. Louis. "Some physicians and insurance companies limit patient access to epidurals because they srongly believe tha epidurals can prolong labor, "Dr. Fogel said. "Delaying or withholding an epidural forces the pregnant woman to suffer needlessly and does not lower the cesarean rate." Each year, about one-million women choose epidural blocks for safe and effective pain relief durig labor.

A study by Dr. Fogel and colleagues at Washington University analyzed labor and delivery data on 7,000 patients. The researchers compared the cesarean rates among first-time mothers during the 12 monts before and the 16 months after epidural analgesia became available on request at the hospital. They found no significant differences in cesarean section rates before and after the services introduction. "Epidural analgesia did not stop normal labor or cause cesarean deliveriew, because the rate of cesareans did not change," Dr. Fogel said.

Women may still require cesarean delivery following epidural blocks, but no direct cause-and-effect relationship has ever been established. "labor epidural anlagesia can be associated with , but does not cause, cesarean section delivery," Dr Fogel said. "An abnormal labor can produce extreme pain for mothers, and this pain leads women to ask for epidurals," he said.

"Our study has the advantage of following cesarean rates before and after the introduction of a popular epidural service," Dr Fogel said. "Since patient demographics and cesarean section rates did not change, we can safely and accurately conclude that the total number of cesarean delieveries performed was not affectred by the availability of epidural analgesia."

Similar findings emerged from an analysis of data on more than 13,000 first-time mothers who gave birth between 1989 and 1995 at St. Luke's Roosevelt Hospital Center, a teaching hospital of Columvia University in New York City.

The analysis showed that themother's age, the baby's birth weight and use of the laborinducing drug oxytocin increased the women's risk for cesarean sections. "Not only was epidural analgesia not a significant risk factor but it was associated with slightly decreased cesarean section delivery risk." anesthesiologist David J. Birnbach, M.D., said.

By relieving pain, epidural analgesia may help some patients relax and this relazation could facilitate labor, Dr. Birnbach said. "We're not suggesting the technique will prevent cesarean sections," he stressed, "but in our practice, epidurals are clearly not a cause." In addition, the use of epidural analgesia almost doulbed at the hospital during the five years studied (from 37% to 68%) but the percentage of cesarean sections deliveries did not increase, Dr. Birnbach said.

A third study at Boston's Beth Isreal Deaconess Medical Center reviewed the labor and delivery records of more than 2300 women who recieved ultra-low dose solutions of epidural medications. The ultra-low dose epidurals allow many women's albor to proceed comfortable, Stephen D. Pratt, M.D., said. For women requireing more apin relief, additional medication can be given by the same epidural route.

The Boston study showed that women who needed additional pain relief beyond the ultra-low dose wre more likely to have cesareans. Women who needed more than two additional doses were twice as likely to require a cesarean section as those who do not. "The slow, abnormal labor that leads to cesarean section is more painful than normal labor and therefore requires stronger epidural medication," Dr Pratt said. "Epidural do not cause cesarean sections. Rather women who have abnormal labor may be in more pain and therefore are more likely to need an epidural and stronger medication."

The above three studies were retrospective studies done in choice situations/hospitals that had actively taken a new approach to reducing cesarean sections as well as hospitals that maintain such high cesarean section rates that the comparisons would be

insignificant due to cesarean rates of over 30%.

The only prospective study was the fourth one, conducted at the University of Texas Southwestern Medical Center in Dallas.<sup>6</sup> Seven hundred, fifteen women of mixed parity in spontaneous labor at full term were randomly assigned to receive either epidural anesthesia (EA) or patient-controlled intravenous meperidine analgesia (PCMA). Epidural analgesia was maintained with a continous infusion of 0.125% bupivacaine with 2 pg/ml fentanyl. Patient controlled analgesia was maintained as 10-15 mg meperidine given every 10 minutes as desired by the patient using a patient-controlled pump.

A total of 358 women were randomized to receive epidural anesthesia and 243 (68%) complied. Similarly, 357 women were randomized to receive patient-controlled analgesia, and 259 (73%) complied with that protocol. Five women randomized to PCMA requested epidurals. Based upon an intent to treat analysis, there was no difference in the rate of cesarean deliveries between the two groups (EA, 4%, 95% CI: 1.9-6.2%; PCMA, 5%, 95% CI: 2.6-7.2%. Women in the epidural group reported lower pain scores during labor and delivery.

What is amazing is that this study was used to argue that epidurals did not increase risk for cesarean birth. What is lacking, of course, is a reasonable control group, such as a doula. When one looks at the amazingly high amounts of meperidine that women could self-administer, it is no wonder that so few requested an epidural, since they could hardly be expected to be very alert. A woman could receive 90 mg of meperdine per hour. In actuality, the average amount of meperidine a woman self-administered was 200 mg with the highest amount being 500 mg. To give a sense of the amounts being given here, routinely in the emergency department, for treating ureterolithiasis (kidney stones), which most women agree is a more severe pain than labor, I would rarely administer more than 150 to 200 mg of meperidine over 12 hours. The average length of labor during which these women received their meperidine was under 12 hours. No one has asked the question of how such a massive dose of meperidine would affect the cesarean rate.

The authors stated, "Patient-Controlled intravenous analgesia is widely used in the United States to manage postoperative pain, although use during childbirth has been limited. One concern is newborn respiratory depression from increased narcotic administration to the mother. Many women in our study used more than 200 mg of meperidine during the course of their labor, but only 3.4% of infants were given naloxone to reverse respiratory depression. The mothers were visibly sedated but were invariably arousable and none experienced respiratory depression."

Since neither of us have never had to give an infant naloxone in over 1000 deliveries, we wonder what the indications would actually be. We suspect these infants were quite depressed to receive naloxone. Our experience with patient controlled analgesia is that the reason the patient stops pushing the button is that she gets so high a dose that she falls asleep. I suspect the mothers were more compromised than the authors think, but none had to be intubated or artificially ventilated, therefore, "none experience respiratory depression."

The authors also under-emphasized the fact that all patients were enrolled at the same time in an aggressive program to reduce cesarean birth, consisting of:

1. No use of electronic fetal monitoring, even for epidurals (except for one test strip on admission), thereby necessitating nurse auscultation of the fetal heart rate and one-on-one patient care, both well known to reduce the cesarean rate.

- 2. No patient admitted to the hospital before 4-5 cm of cervical dilation, also known to lower the cesarean rate.
- 3. No drugs or epidurals until the woman was 5 cm dilated, also known to reduce the cesarean rate.
- 4. All births attended by CNMs, which is known to reduce the cesarean rate by one-third of what obstetricians would do. For example, a study from Los Angeles County-USC Hospital showed a 4% cesarean rate in a 95% Hispanic population when they were attended by nurse-midwives.<sup>2</sup>
- 5. Use of a black and Hispanic population. In an editorial discussion, the authors, themselves, comment on black and Hispanic populations having historically lower cesarean rates

The authors' real conclusions are this: If you do everything possible to reduce the cesarean rate for all patients, and then, if you compare epidural anesthesia with high dose, self-administered narcotic analgesia, there is no difference in the cesarean rate. This is not really a very outstanding conclusion, though the popular press read this result as saying epidural anesthesia is now proven safe and unlikely to increase the cesarean rate (without addressing the question, "over what?"

Some infants (0.8%) in the epidural group also required naloxone. Two transfers to NICU occurred in the epidural group and 3 in PCMA group.

Looking just at those who had epidurals vs. those who didn't, epidurals prolonged the first stage of labor and increased the incidence of oxytocin administration. Fever developed in more women during epidural anesthesia. There was no difference in the number of cesareans in the epidural vs. the PCIA group (the range from 3% to 7% cesarean rate).

Regarding other complications, 24% of women having epidurals had fever compared to 6% in PCMA. Nine percent had forceps with epidural compared to 3% with PCMA. There was a15-19% range of meconium during labor (not different between groups), which we find rather high. There was a rate of 1.2-1.8% of infants suffering meconium aspiration (not different between groups), but also rather high in our experience.

## 2. Significant low blood pressure (hypotension):

Significant low blood pressure is a complication of epidural anesthesia.<sup>1</sup> The ways that epiduralized patients must lie accentuate this. Their position is limited since they are essentially paralyzed people for the duration of the epidural. Hypotension occurs among almost one-third of patients with serious hypotension occurring about 12% of the time.

Maternal hypotension is a major risk for the baby. The epidural blocks the nerves which regulate blood pressure. It causes the blood in the body to pool, keeping it from being pumped around the body in the proper manner. The arteries dilate and relax their usual, necessary level of tension, making it difficult for the heart to pump blood to the baby. These changes lead to a decrease in the output of the mothers heart. Less blood per unit time can reach the placenta and therefore the baby.

The baby is completely dependent on the mothers heart to pump blood to the placenta to satisfy its needs. All of its oxygen comes across from the placenta. All of the food for its brain and other organs comes across the placenta. Brains cannot live without a

relatively constant supply of oxygen and glucose. Without this they become damaged.

A good blood flow is needed to the uterus between contractions so it can get fresh oxygen. During the contraction, blood flow to the uterus is cut off by the muscles contracting. When the contraction stops, the uterus must quickly refill with fresh blood containing oxygen for the baby. If the amount of blood flowing to the uterus is reduced, the baby may not be able to get the oxygen it needs. Then what is called fetal distress may occur. The babys system does not get enough oxygen and goes into distress. Its blood retains excess acid, the oxygen levels go low and tissues and vital organs begin to fail from excess acid, lack of oxygen and lack of fuel

Animal studies have shown that lack of oxygen to the baby (called fetal hypoxia) can cause significant damage to the baby's brain even without the pH of the baby's umbilical cord blood being affected.<sup>9</sup> (The pH of the babys umbilical cord blood at birth is usually used as an indicator of whether or not fetal hypoxia has occurred.)

Severe low blood pressure can also result from compression of the mothers blood vessels (aorta and vena cava) since all mothers must lie essentially flat on their back after epidural anesthesia (they cannot feel or move their back, pelvis and legs).<sup>10</sup>

## 3. Fetal distress:

Fetal heart rate decelerations can occur following the use of epidurals.<sup>1</sup> Babies can develop fetal distress after epidural anesthesia.<sup>11</sup> This may be caused by the mothers blood pressure getting so low that blood cannot be adequately pumped into the uterus to deliver oxygen to the baby. As we mentioned above, epidurals make it difficult for the muscles in the arteries of the lower body to respond and to keep blood adequately flowing through the body. The ability of the heart to respond to changing needs of the body is impaired.<sup>12</sup> Eberle and Norris<sup>1</sup> suggest that [i]nduction of maternal analgesia may transiently alter the balance between factors encouraging and discouraging uterine contraction. A temporary increase in the uterotonic effects of endogenous or exogenous oxytocin may then produce a tetanic contraction with subsequent decrease fetal oxygen delivery and resultant fetal bradycardia.

Most babies of mothers receiving epidural anesthesia develop episodes of slow heart rate (bradycardia).<sup>13</sup> While this does not usually affect the healthy baby, it can be disastrous for the baby that is alreay compromised from some other problem (often unknown to the doctors).

Adverse effects on the baby indicative of insufficient oxygen reaching the baby (late decelerations) can occur. These changes may also result from a toxic effect to the baby of the local anesthetic given in the epidural.

The transient low blood pressure which always occurs after epidural anesthesia has been found to lead to significantly lower the babys blood pH.<sup>14</sup> This indicates excess blood acid, usually meaning that the baby is not getting enough oxygen. Anesthesiologists don't think that this makes any difference in the babys outcome, but we suspect, if we studied babies already at risk for other reasons, we would find that epidural significantly worsens compromised babies and may lead to a Cesarean birth when the baby might have otherwise tolerated a vaginal birth. We suspect that more detailed research would identify a group of babies who would have tolerated unmedicated, normal birth, but who are unable to handle the added stress of the epidural, leading in the worst causes to death or permanent disability.

#### 4. IV Cannulation:

Accidental injection of the anesthetic solution into the blood stream can occur and can cause the mother to twitch, have convulsions, or lose of consciousness. Seizures can occur from the toxic effects of the anesthetic agent entering the blood stream.<sup>15</sup> Local anesthetic toxicity occurred among 12 women in 1000 epidurals.<sup>16</sup>

#### 5. Trauma to blood vessels:

Trauma to blood vessels can occur as a result of epidural anesthesia.<sup>17</sup> In one study, bleeding in the spinal column and unintentional placement of the catheter into an artery or vein occurred 0.67% of the time (67 women of every 1000 epidurals).<sup>18</sup> The catheter actually escapes outside of where it is supposed to go 1 to 6% of the time.<sup>19</sup>

Hemorrhages can occur around the spinal cord and even within the skull following epidural anesthesia.<sup>20</sup> These were associated with persistent backaches or headaches. Failure to treat these problems usually results in permanent paralysis. Surgery must be performed within 8 hours of the onset of paralysis or the prognosis is poor. Chronic subdural hematoma has resulted from epidural anesthesia and has even presented as post-partum psychosis.<sup>21</sup>

#### 6. Punctured dura:

The actual dura may be punctured as a result of epidural anesthesia. Because of the large size of the needle used, severe headache may also result. Dural punctures have been found to occur about 1.8% of the time.<sup>22</sup> Unintentional dural puncture occurred in 61 of 1000 epidurals in a University hospital (resulting in spinal anesthesia).<sup>23</sup>

# 7. Infection:

An infection can develop at the site of injection. Bacterial meningitis can occur from contamination during placement of the epidural.<sup>24</sup> An abscess can also form at the site where the epidural catheter is placed.<sup>25</sup>  $\frac{26}{26}$ 

# 8. Backache:

Backache is a common complication. Back pain commonly occurs after epidural anesthesia (18.9% of the time<sup>27</sup>). Upper back pain can happen at some distance from the site where the epidural is injected.<sup>28</sup> The back pain can last very long-term.<sup>29</sup> Nineteen percent of women had long-term backache after epidural anesthesia.<sup>30</sup> It probably results from a combination of its effects on the nerves and from extreme postures and stretching that occurs after the epidural during labor.

Low back pain after epidural anesthesia for childbirth is also frequently mentioned.<sup>31</sup>

### 9. Broken catheters:

Occasionally the catheter has broken and a small piece is left in place. It usually causes no ill effects.

## **10. Abnormal uterine contractions:**

Uterine contractions can become weaker and less frequent. An oxytocin infusion is then necessary to improve labor and produce good strength contractions Mothers having

epidurals have longer labors and have a higher incidence of the use of oxytocin than mothers having non-medicated deliveries.<sup>32</sup>

There are important risks of giving oxytocin also. Administration of this hormone to the mother during labor can cause:

- 1. Dangerously high blood pressure.
- 2. Abnormal heart rhythms.
- 3. Nausea and vomiting.
- 4. Sustained uterine contractions which last too long and result in the baby going into distress from lack of oxygen. When this is too severe, the uterus can rupture. The epidural can mask the strength of the uterine contractions so that no one knows that how strong they are, making uterine rupture more possible.
- 5. Hemorrhage around the brain.
- 6. Retention of water leading to convulsions and coma.
- 7. Bleeding in the pelvis and increased incidence of postpartum hemorrhage.
- 8. Death of the baby.
- 9. Jaundice of the baby.

## 11. Second stage labor effects:

With large doses the patient loses the desire and the ability to bear down and push. This results in an increased use of forceps and vacuum extractions over women having unmedicated deliveries.<sup>33</sup>

#### 12. Inadequate pain relief:

The epidural is generally inadequate 7.1% of the time leading to supplementation with intravenous pain medication 4.0% of the time and a general anesthetic 3.1% of the time (in one study).<sup>34</sup>

### 13. Accidental spinal anesthesia:

When an epidural accidentally turns into a spinal anesthetic, many complications can occur:

- 1. Postspinal headaches.
- 2. Dysfunction of the bladder is frequent
- 3. Occasionally numbness and tingling (paresthesias) of the lower limbs and abdomen develop, and sometimes there is a temporary loss or diminution of sensation in these areas.
- 4. Unilateral footdrop (paralysis of the muscle that lifts the foot) has occurred.
- 5. Permanent nerve damage (conditions called chronic, progressive adhesive arachnoiditis or transverse myelitis) can occur. These lead to paralysis of the lower parts of the body.

- 6. Deaths have been reported.
- 7. Difficult breathing
- 8. Increased incidence of forceps deliveries.

The reliability of spinal anesthesia with 5% hyperbaric lignocaine was studied among 30 patients undergoing elective Cesarean. Twelve patients had hypotension and four developed severe postspinal headaches. The block progressed to the C2 dermatome in four patients and was associated with dysphagia. This was totally unpredicted and was thought due to altered cerebrospinal fluid dynamics in late pregnancy.<sup>35</sup>

# 14. Maternal heart attack or spinal cord ischemia:

The lack of ability of the heart to pump blood around the body (from low blood pressure or pooling of blood) can become so severe that a heart attack occurs or the spinal cord will suffer damage from not enough blood reaching it.<sup>36</sup>

## **15. Asthmatics:**

Asthmatics can get suddenly worse during epidural anesthesia $\frac{37}{3}$  with more wheezing and inability to breath.

## **16. Medication interactions:**

A hidden danger of epidural anesthesia is its interaction with medications (prostaglandins) commonly used to soften the cervix and start labor. The use of prostaglandins is common at hospitals and creates a potentially dangerous situation in which the usual medications used to treat low blood pressure during labor will no longer work.<sup>38</sup>

## 17. Interactions occur with other illnesses:

As an example, women who have migraines can have more visual disturbances after epidurals.<sup>39</sup>

# 18. Maternal fever:

Maternal fever and even the severe condition called malignant hyperthermia (dangerously high fever) can result.<sup>40 41</sup>

### **19. Respiratory arrests:**

Mothers can stop breathing (respiratory arrest)<sup>42 43</sup> and can experience other breathing difficulties.<sup>44</sup> Greenhalgh<sup>\*</sup> reported a 19 year old obstetric patient who had a respiratory arrest shortly after receiving intrathecal sufentanil and bupivacaine as part of a combined epidural/spinal technique for pain relief.

Other neurological disabilities (including a condition called Horners syndrome) can develop along with hoarseness (from even just one dose of epidural anesthetic).<sup>45</sup> Clayton<sup>46</sup> reported an incidence of Horner's syndrome during epidural anesthesia for elective Caesarean section of 4%. The incidence of Horner's syndrome with epidural anesthesia for vaginal delivery was 1.33%. They found it impossible to predict which patients would develop a Horner's syndrome. Even the nerves to the face can be blocked, sometimes temporarily, sometimes permanently.<sup>47</sup> Tremors and shakes can occur.<sup>48</sup> <sup>49</sup>

Paresthesias (persistent tingling from sensory nerves) occurred in 0.16% of patients in one study (1.6 per 1000) with an incidence of persistent neuropathy of 0.04% (4 per 10,000).<sup>50</sup> Four of these patients had a neuropathy which eventually resolved. In another study 3.0% of patients had tingling of the hands or fingers, while 26 of almost 5000 women had persistent tingling or numbness in the lower back, buttocks or legs.<sup>51</sup>

Dizziness and fainting can become a problem after epidurals. One study found these symptoms persisting in 2.1% of women.  $\frac{52}{2}$ 

# 21. Nausea and vomiting:

Twenty to 30 percent of women experience nausea after epidural anesthesia, while 3 to 7% have vomiting.  $\frac{53}{2}$ 

# **22. Allergic conditions:**

A dangerous allergic condition with shock (called anaphylaxis) can occur.<sup>54</sup> The woman develops a red rash (erythema), itches, and her lungs fill up with fluid (pulmonary edema). Excessive lung fluid is also found in the babies in these cases.<sup>55</sup>

#### 23. Heart problems:

Mothers can experience excessively slow heart rates (bradycardia), heart block in which the electrical activity of the chambers of the heart become dissociated and sometimes even stoppage of the heart (cardiac arrest).<sup>56</sup>

## 24. Headache:

Headache after epidural is a persistent problem that is more pronounced in younger patients.<sup>57</sup> One study found its incidence after epidural anesthesia to be 4.6%, significantly more often than women not having epidurals.<sup>58</sup> It usually occurs from the effects of puncturing the dura. Headache can also occur from air getting into the spinal fluid (called an iatrogenic pneumocephalus). The air is introduced into the spinal fluid and column when the test dose is given that is assumed to be in the extra-dural space. When the person giving the epidural feels a loss of resistance to the injection of air, this is when a pneumocephalus can occur. The patient that was described complained immediately of severe headache on both sides of her forehead followed by vomiting. The baby had to be delivered by Cesarean with general anesthesia. The patients headache resolved in 24 hours after Cesarean.

Of 34 women with spinal headache (from 4766 epidurals), nine had long-term disability from headache. Five of these were from accidental dural puncture and four occurred after accidental spinal block.<sup>59</sup>

# 25. Motor blockade:

Epidural anesthesia can produce motor blockade, resulting in temporary paralysis, even of respiratory muscles. $\frac{60}{2}$ 

#### 26. Use in VBAC:

Epidurals are sometimes used with women desiring VBAC. Leung, et al.<sup>61</sup> studied the maternal and fetal consequences of uterine rupture during VBAC. They concluded that significant neonatal morbidity occurred when > or = 18 minutes elapsed between the onset of prolonged deceleration and delivery. In 106 cases of uterine rupture at their institution between Jan 1, 1983 and June 30, 1992, seven charts were incomplete and excluded; of the remainder, 28 patients had complete, 13 patients had partial, and 58 patients had no fetal extrusion into the maternal abdomen. Maternal characteristics or intrapartum events were not predictive of the catastrophic extent of uterine rupture. There was one maternal death. Complete fetal extrusion was associated with a higher incidence of perinatal mortality and morbidity.

#### 27. Technical considerations:

Epidural anesthesia is a technical procedure that requires significant skill to place correctly. Many papers document the technical aspects of this procedure which are not insignificant. For example, 23% of epidural catheters inserted more than 2 cm into the epidural space required manipulation. Epidural catheters inserted 8 cm within the epidural space were more likely to result in iv cannulation. Epidural catheters inserted 2 cm within the epidural space were more likely to become dislodged. Epidural catheters inserted 2 to 4 cm within the epidural space required replacement more often than catheters inserted deeper.  $\frac{62}{2}$ 

#### 28. Herpes simplex assocation:

Epidural analgesia is associated with recurrence of herpes simplex blepharitis after cesarean section when epidural morphine is given.  $\frac{63}{2}$ 

#### **Case Examples (mild problems)**

Here is an example of a 30 year old woman having her first baby who was admitted to the hospital at 2 cm dilation at  $11:05 \text{ pm.}^{64}$  By 4:30 am, she was 4 cm dilated with her waters broken and requested epidural anesthesia. Her mother and her husband were in attendence coaching her. The epidural was started at 5:01 am and within 30 seconds, the patients heart rate began to climb steadily and precipitously from 88 to 174, levelling off at that rate.

The certified registered nurse anesthetist (CRNA) discovered that the patient had previously experienced heart palpitations: when stressed or with heavy exercise. She had begun to feel mild nausea and dizziness. Oxygen was administered and an iv drug (adenosine) was given. A second dose followed five minutes later. The abnormal heart rate (a supraventricular tachycardia) returned to normal and the woman had a normal vaginal delivery within 6 hours of this episode. This occurred presumable from a sensitivity to medication placed through the epidural catheter. When complications such as this occur, fetal scalp electrodes are usually placed to monitor the babys EKG. The therapy sometimes causes severe hypotension.

A case has been reported in which a 24 year old woman with a past history of mild backache had an epidural anesthesia. She had an acute vagal reaction with loss of

consciousness and her head falling forward. Thirty-six hours later, she complained of severe pains all over her spine, together with sciatica and spasm of the muscles on either side of the spinal column (paravertebral muscles). None of these symptoms responded to drug treatment. The pain eventually disappeared after she wore a cervical collar, taking anti-inflammatory drugs and having spinal manipulations (what chiropractors and osteopaths do) It was thought that her backache was due to what is called a posterior articular joint syndrome in which the forward fall of her head strained the posterior joints of the spinal column.<sup>65</sup>

#### Permanent disability from epidural anesthesia

a. A disabling condition called spinal arachnoiditis can develop after epidural anesthesia. Of 6 such women, 3 were permanently confined to a wheelchair three years after their initial evaluation.<sup>66</sup> None of these patients had any prior spinal surgery or trauma or problems with the spinal cord including previous hemorrhage, infections or other known causes of arachnoiditis. They had no neurological symptoms prior to epidural anesthesia. The diagnosis was confirmed by a medical test called myelography in all cases. The epidurals were uneventful and performed according to standard methods.

Arachnoiditis is probably caused from the epidural injection of foreign substances (the anesthetic itself or contaminants in the solution) into the spinal canal.

Subarachnoid cysts can occur in the spine from arachnoiditis produced from the epidural anesthetic.  $\frac{67}{2}$ 

b. Paralysis can occur.<sup>68</sup> The injection of the local anesthetic into the epidural space can result in the veins becoming engorged, the spinal cord suffering from a lack of oxygen (hypoxia) and the woman developing acute neurological problems. Some of these deficits can become permanent.<sup>69</sup> Paralysis can also occur from bleeding into the area during the epidural injection with the formation of a pocket of blood pressing on the spinal cord (hematoma). It can also occur from infection or trauma.

Cranial nerve paralysis can occur at quite a distance from the site of the epidural. This is thought to occur from traction on the spinal cord.<sup>70</sup>

Paralysis can occur from a condition called anterior spinal artery syndrome after epidural anesthesia during labor.<sup>71</sup> Paralysis can occur when the blood flow to the spinal cord becomes so limited that tissue dies. This is called an infarction. A case report of an infarction after epidural anesthesia has been published in which leg paralysis occurred and did not recover. A loss of sensation to pain and temperature also occurred to the level of the mid-chest which partially resolved.<sup>72</sup>

Of 108 non-fatal complications in one study, five were associated with permanent disability.<sup>73</sup> These included damage (neuropathy) to a single spinal nerve, acute toxicity from the local anesthetic, and problems associated with accidental puncture of the dura to become a spinal anesthetic.

Another patient developed paralysis after epidural anesthesia probably due to the anterior spinal artery or central arteries being blocked during the epidural and leading to death of part of the spinal cord.<sup> $\frac{74}{14}$ </sup>

Neuropathy is a condition in which sensory changes occur (loss of sensation or hypersensitivity to sensation) with or without chronic pain. Neuropathy occurs after epidural anesthesia. It can occur from thrombosis of an artery from trauma from the epidural injection or from the catheter. A lack of adequate blood flow (and therefore oxygen) is called ischemia. This can cause neuropathy also.<sup>75</sup>

#### Deaths from epidural anesthesia

Here are some examples of woman who have died from epidural anesthesia to illustrate the dangers.

A healthy, 31 year old woman having her third child requested epidural anesthesia and developed an acute condition of fluid in the lungs (pulmonary edema). She could not be successfully resuscitated. The baby also died.<sup>76</sup>

Sudden stoppage of the heart (cardiac arrest) can occur during epidural anesthesia.<sup>72</sup> <sup>78</sup> along with other heart rhythm changes.<sup>79</sup> Sudden cardiac arrest may be caused by air getting into veins during placement of the epidural.<sup>80</sup>

Respiratory insufficiency can occur and cause death. In one case report, the patient initially developed pain in the shoulder-neck region after epidural anesthesia, followed by fever and an elevated white blood count. This led to a high-level (arms and legs) paralysis with an inability to breath. Many problems then developed with the heart and arterial system. An abscess was found and the patient was eventually stabilized with antibiotics. The patient required chronic mechanical ventilation and died of recurrent pneumonia after 5 months of intensive care. The incidence of breathing difficulties in one study was 0.54%, although only 5% of those patients required prolonged artificial ventilation. Total spinal anesthesia occurred in 0.013% of the epidurals but more than half of these auses required intubation and prolonged mechanical ventilation. Partial spinal anesthesia (sub-arachnoid block) occurred in 0.04% of the cases.<sup>81</sup>

Women are almost never given informed consent for epidurals. Even if they were just read two paragraphs from the package insert that comes with the medication used for epidurals (manufactured by Abbott Laboratories), they might think twice. The package insert states:

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal or pudendal anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity....Adverse reactions in the parturient, fetus and neonate involve alternations of the central nervous system, peripheral vascular tone and cardiac function.... Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Who would sign a consent if it included the above language? The degree to which the facts about the risks of epidural anesthesia are hidden from women in labor is astonishing.

Mothers who have a fever are significantly more likely to have had epidural anesthesia.<sup>82</sup> Therefor increasing the incidence of septic workups on newborns and the subsequent complications of this procedure.

We would hope that pregnant women would have a more informed explanation of the risks of epidural anesthesia than what is currently given, and would suspect that many would make other choices if true informed consent was given (before labor, when the woman still has time to prepare to cope with childbirth pain in other ways).

## **Critique of 3 other studies**

As we said the study we just discussed was the only prospective study. The other three studies are papers not yet published so we can only comment on the abstracts of these studies, they were "presented" at the conference of the American Society of Anesthesiologists in November of 1997. Presented means that the paper was talked about at the conference and has not necessarilly been accepted by a major medical journal for publication as of yet and may/or may not be.

## 1st additional study:

**TITLE:** Does epidural analgesia protect against cesarean section in nulliparous patients?

**AUTHORS:** DJ Burnbach, MD, A Grunebaum, MD, DJ Stem, MD, B Katgaem MD, MM Kuroda, MPH, DM Thys, MD

**AFFILIATION:** Department of Anesthesiology and Ob/Gyn, St. Luke's-Roosevelt Hospital Center, College of Physicians and Surgeons of Columbia University, New York, NY

**INTRODUCTION:** Recent articles have suggested that epidural analgesia may increase the risk of cesarean section. (1,2) In an effort to evaluate whether epidural analgesia during labor is associated with an increased risk of cesarean section at our institution, we evaluated the labor data of unlliparous patients who delivered at the hospital between 1989-1995.

**METHODS**: From January 1, 1989 -December 31, 1995, there were a total of 31,670 deliveries at the St. Luke's-Roosevelt Hospital Center. The 13,203 nulliparous patients who delivered under the care of an obstetrician during that period of time constituted the study population. The following were the independent variables: type of labor analgesia administered, patient age, obstetric care provider (private vs. non-private), birth weight, and use of oxytocin for stimulation or induction. The dependent variable was the delivery mode. A non-hierarchical logistic regression was performed to determine which of these independent variables contributed to the risk of cesarean section.

**RESULTS:** Logistic analysis demonstrated that the highest risks for cesarean section were associated with oxytocin induction and maternal age. As shown in Table 1, other significant predictors of cesarean delivery were oxytocin for stimulation, patient status (private patients were at an increased risk of cesarean section) and birth weight. Epidural analgesia, on the other hand, was associated with a slightly decreased risk for cesarean section. For example, patients under 30 years of age who were induced with oxytocin who received epidural analgesia had a 32% cesarean section rate (230/719) versus a 39.1% cesarean section rate (70/179) for the same group of patients who did not receive an epidural anesthetic. Patients greater than 29 years of age who were induced with oxytocin and received an epidural had a 45.4% cesarean section rate (114/251) versus a 58% cesarean section rate (51/88) for the same group of patients who did not receive an epidural.

Table 1:

Independent Variables	Odds Ratio	Confidence Interval
Oxytocin Induction	1.93	1.70 - 2.19
Maternal Age (per 10 years)	1.60	1.53 - 1.68
Birth Weight (per 1000g)	1.20	1.13 - 1.27

Oxytocin Stimulation	1.17	1.06 - 1.30
Patient Status (pvt. vs clinic)	1.10	1.01 - 1.16
Epidural Analgesia	0.89	0.81 - 0.97

**DISCUSSION:** Our data support other studies that have shown an increased risk of cesarean section with use of oxytocin, increased maternal age, and private patient status.(3) When controlled for other variables, the administration of epidural analgesia was associated with a decreased risk of cesarean section. Based on our data, we suggest that epidural analgesia as practiced at our institution, is associated with a decrease in cesarean section rate in nulliparous patients.

- 1. Obstet Gynecol 1996;88:993-1000
- 2. Am J Obstet Gynecol 1993;169:851-8
- 3. Am J Obstet Gynecol 1993;168:1881-5

# **CRITIQUE:**

A major statistical problem with the study, which prevents the authors from making the conclusions they have made, is the failure to consider the interaction between epidural anesthesia and oxytocin stimulation. Many studies have shown that epidural anesthesia increases the need for oxytocin stimulations [refs]. A proper statistical procedure would have been to use an interactive term for epidural and oxytocin stimulation.

I would have started with a multivariate analysis of variance which would have considered the interaction between epidural anesthesia and the other variables. The authors believe (erroneously) that they are dealing with independent variables. Clearly we all know that there is an association between oxytocin induction and epidurals (more difficult labors; more likely to have an epidural), maternal age (younger and older mothers are more likely to have epidurals), oxytocin stimuation (women who have epidurals are more likely to need oxytocin stimuation because of the desultory effect of the epidural on uterine contractions, private patients are more likely to have epidurals.

The more sophisticated approach to their paper would have been to use a technique such as structural equations modeling (LISREL, or related procedures) to test paths of effects. For example, one can test the hypothesis that epidurals affect the cesarean rate through their effect on the need for uterine stimulation. That could still be done with the authors' data, and we plan to challenge them to an independent data analysis (by our colleagues at the University of Pittsburgh) using path analysis to test these hypotheses.

Simply using logistic regression in this context was inappropriately simplistic, but done probably because it supported their bias (epidurals are good!). I suspect the authors are well-informed and have excellent biostatistical consultation, and chose not to report these other analyses that they probably did, because these other analyses did not support their position.

I would draw your attention to another part of the abstract. Is it reasonable practice to do cesareans on 58% of women who are older than 29 years and are being induced? Are these numbers generalizable? I was shocked to read this figure. In all my experience in obstetrics, I can't imagine how you can perform a cesarean on 58% of the women over age 29 whom you are inducing.

I would very much like to see their criteria for cesarean. With such high rates (45% in the epidural group and 58% in the non-epidural group), I question how generalizable these results are to good practice elsewhere. Perhaps in an environment (consider how stressful this environment must be) in which such high cesarean rates occur, epidurals do decrease the risk for cesarean if you are being induced, but I can't believe that such high cesarean rates constitute safe and prudent practice.

I would like to see their overall complication rates, including post-partum infection and the backache/headache complications of epidurals. I suspect their morbidity is quite high.

# 2nd & 3rd additional studies:

Two other studies shed some light on this debate. The first is Newton ER, Schroeder BC, Knape KG, Bennett BL. **Epidural analgesia and uterine function.** Obstet Gynecol 1995; 85:749-55.

"Continuous epidural analgesia with bupivacaine and fentanyl did not result in a change in myometrial contractility in the first hour after initiation of analgesia. However, despite more oxytocin therapy, the rate of cervical dilation was significantly slower in the epidural group than in the nonepidural group (1.9 versus 5.6 cm/hr, p < 0.001). Operative deliveries were more common in patients with epidural analgesia than in those without it (12 of 62 versus 2 of 124, p < 0.0001). After epidural analgesia, myometrial contractility is maintained with oxytocin, but the ability of the uterus to dilate the uterus is reduced significantly."

Also important, Albers LL, Anderson D, Cragin L, Daniels SM, Hunter C, Sedler KD, Teaf D. **The relationship of ambulation in labor to operative delivery.** JNM 1997; 42(1):4-8.

"Women who ambulated for a significant amount of time during labor (compared with those who did not ambulate) had half the rate of operative delivery (2.7% versus 5.5%)." It's very hard to ambulate with either an epidural or PCIA.

Two others studies have been widely quoted in the popular press. They included a study by Dr. Steven Fogel, an anesthesiologist at Washington University School of Medicine, in St. Louis. Dr. Fogel looked at data on 7,000 patients delivering over a 28 month period at his hospital. He compared cesarean rates for first time mothers before the introduction of an epidural on demand anesthesia service to cesarean rates after the introduction of the service, finding no change. What isn't reported is how obstetrical practices changed during this time interval, a very significant factor. Such historical studies are notoriously unreliable because policies change so rapidly in obstetrical management. Without such information, the study is meaningless.

The final study was done at Boston's Beth Isreal-Deaconess Medical Center by anesthesiologist Steven Pratt. This study reviewed the labor and delivery records of more than 2300 women who received ultra-low dose solutions of epidural medications. The study showed that women who needed additional pain relief beyond the low-doses were more likely to have cesareans than women who did not. Dr. Pratt argued that it was harder labors that caused cesareans and not epidurals. This study was so anecdotal as to be hardly worth commenting upon. What Dr. Pratt failed to note was that several others studies have shown that patient satisfaction with low-dose epidurals is very low and that more than half of women have additional medication. Pratt's study actually supports the point of view that epidurals lead to increased cesareans, when this information is taken into account.

What is amazing is the propagandizing that went on in the press. The gold standard in medicine consists of randomized, controlled trials. These have been done and do generally show increased cesarean rates. To try and argue against these much better quality studies with retrospective studies using historical controls is poor science, but clearly good propaganda. To conclude we list some of these studies and their conclusions:

Prospective Clinical Trials Investigating the Association between Epidural Analgesia

and Cesarean Birth Rates by Randomizing Women to a Narcotic versus an Epidural Group:

Reference and Parity Sample Size Relative Risk of Cesarean Birth with Epidural Analgesia (95% CI)

Combined 111 2.8 (0.8-10.0)
Nulliparous 93 11.4 (5.8-16.9)\*
Nulliparous\*\* 693 2.6 (1.5-4.3)\*

Parous\*\* 637 3.8 (1.3-11.0)\* Combined\*\*\* 869 2.3 (1.3-4.0)\* All three prospective trials combined 1073 2.5 (1.6-4.0)\*\*\*\*,\*

- \* Relative risk is statistically significant at least at p < 0.05
- \*\* This represents the odds ratio for all women in the study adjusted by multivariate logistic regression analysis.
- \*\*\* The cesarean birth rate was significantly greater (p = 0.002) in the epidural group (9%, 39/432) compared with the narcotic group (4%, 17/437).
- \*\*\*\* Comparison of the proportions by Mantel-Haenszel yields a chi-squared of 18.1 and a p-value of 0.00003.

1. Phillipsen T, Jensen NH. Epidural block or parenteral pethidine as analgesic on nulliparous labor; a randomized study concerning progress in labour and instrumental deliveries. Eur J Obstet Gynecol Reprod Biol 1989; 30:27-33.

2. Thorp JA, Hu DH, Albin RM. The effect of intrapartum epidural analgesia on nulliparous labor: A randomized prospective trial. Am J Obstet Gynecol 1993; 169:851-858.

3. Ramin SM, Gambling DR, Lucas MJ. Randomized trial of epidural versus intravenous analgesia during labor. Obstet Gynecol 1995; 86:783-789.

#### References

- 1. Eberle RL, Norris MC. Labour analgesia: A risk-benefit analysis. Drug-Saf 1996; 14(4):239-251.
- Kantor G. Obstetrical epidural anesthesia in a rural Canadian hospital. Can J Anaesth 1992; 39:390-3.
- Thorp JA, Parisi VM, Boylan PC, Johnston DA. The effect of continuous epidural analgesia on cesarean section for dystocia in nulliparous women [see comments]. American Journal of Obstetrics & Gynecology 1989 Sep;161(3):670-5.
- Adashek JA, Peaceman AM, Lopez-Zeno JA, Minogue JP, Socol ML. Factors contributing to the increased cesarean birth rate in older parturient women. American Journal of Obstetrics & Gynecology 1993 Oct;169(4):936-40
- David J. Birnbach, M.D., Steven T. Fogel, M.D., Stephen D. Pratt, M.D.; New Data Debunks Belief that Epidurals Cause Cesarean sections, San Diego, Press Release, American Society of Anesthesiologists, 1998.
- Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. Cesarean Delivery: A randomized trial of epidural versus patient-controlled meperidine analgesia during labor. Anesthesiology 1997; 87:487-94.
- Twelve Years and More than 30,000 Nurse Midwife-Attended Births: The Los Angeles County + University of Southern California Women's Hospital Birth Center Experience: Journal of Nurse midwifery Vol 39, No 4, July Aug 94.
- 8. Webb and Kantor, 1992
- 9. Haire DB. Obstetric drugs: their effects on mother and child. Encyclopedia of Childbearing, New York: Henry Holt and Company, 1993.

10. [Hetland, et al., 1989]

- 11. [Rosay, et al., 1989]
- 12. [Parnass and Schmidt, 1990]
- 13. [Marx, et al., 1990]
- 14. [Philipson, et al., 1989]
- 15. [Dunne and Kox, 1991]
- 16. [Tanaka, et al., 1993]
- 17. [Skidmore, 1991]
- 18. [Tanaka, et al., 1993]
- 19. [Halpenny, et al., 1992]
- 20. [Schmidt and Nolte, 1992]
- 21. [Campbell & Varma, 1993]
- 22. [Webb and Kantor, 1992]
- 23. [Tanaka, et al., 1993]
- 24. [Berga and Trierweiler, 1989]
- 25. [Goucke and Graziotti, 1990]
- 26. [Sonden, 1991]
- 27. [MacArthur, et al., 1992]
- 28. [Rajanna, 1989]
- 29. [Anonymous, Lancet, 1990a,b]
- 30. [MacArthur, et al., 1990]
- McQuay H, Moore A. Epidural anesthesia and low back pain after delivery (letter). BMJ 1996; 312(7030): 581.
- 32. [Sepkoski, et al., 1992]
- 33. [Sepkoski, et al., 1992]
- 34. [Webb and Kantor, 1992]
- 35. [Bembridge, et al., 1986]
- 36. [Girompaire, et al., 1990]
- 37. [Eldor, et al., 1989]
- 38. [Veeckman, et al., 1989]
- 39. [MacArthur, et al., 1992]
- 40. [Anonymous, Lancet, 1989]
- 41. [Vanek and Valenta, 1989]
- 42. [Fortuna, 1989]
- 43. [Lee and Collins, 1990]
- 44. [Tembo and Hills, 1990]
- 45. [Tabatabia, et al., 1989]
- 46. [Clayton, 1989]
- 47. [Gazmuri, et al., 1992]

- 48. [Branda and Tumbarello, 1990]
- 49. [ Basora, et al., 1990]
- 50. [Tanaka, et al., 1993]
- 51. [MacArthur, et al., 1992]
- 52. [MacArthur, et al., 1992]
- 53. [Chestnut, et al., 1989]
- 54. [Zucker-Pinchoff and Ramanathan, 1989]
- 55. [Thomas and Caunt, 1993]
- 56. [Parnass and Schmidt, 1990]
- 57. [Parnass and Schmidt, 1990]
- 58. [MacArthur, et al., 1992]
- 59. [MacArthur, et al., 1992]
- 60. Greenhalgh CA. Respiratory arrest in a parturient following intrathecal injection of sufertanil and bupivacaine. Anaesthesia 1996; 51(2):173-175.
- 61. [Leung, et al., 1993]
- 62. Eberle and Norris, 1996, op cit.
- 63. DAngelo R, Berkebile BL, Gerancher JC. Prospective examination of epidural catheter insertion. Anesthesiology 1996; 84(1) 88-93.
- 64. [Stickes, 1993]
- 65. [LeBorgne, et al., 1991]
- 66. [Sghirlanzoni, et al., 1989]
- 67. [Sklar, et al., 1991]
- 68. [Parnass and Schmidt, 1990]
- 69. [Sghirlanzoni, et al., 1989 Oct]
- 70. [Whiting et al., 1990]
- 71. [Ackerman, et al., 1990]
- 72. [Gaudin and Lefant, 1990]
- 73. [Scott and Hibbard, 1990]
- 74. [Hachisuka, et al., 1991]
- 75. [Veselis, 1990]
- 76. [Van Zundert and Scott, 1989]
- 77. [Gild and Crilley, 1990]
- 78. [Watanabe, et al., 1990]
- 79. [Elstein and Marx, 1990]
- 80. [Williams, et al., 1991]
- 81. [Xie and Liu, 1991]
- 82. [Klaus et al. 1993:47]