Unintended effects of epidural analgesia during labor: A systematic review

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Epidural analgesia is used by more than half of laboring women, yet there is no consensus about what unintended effects it causes. To evaluate the state of our knowledge, we performed a systematic review of the literature examining the unintended maternal, fetal, and neonatal effects of epidural analgesia used for pain relief in labor by low-risk women. Our review included randomized and observational studies appearing in peer review journals since 1980.

Much of the evidence is equivocal. Existing randomized trials are either small or do not allow clear interpretation of the data because of problems with protocol compliance. In addition, few observational studies control for the confounding factors that result because women who request epidural are different from women who do not.

There is considerable variation in the association of epidural with some outcomes, particularly those that are heavily practice-based. Despite this variation, there is sufficient evidence to conclude that epidural is associated with a lower rate of spontaneous vaginal delivery, a higher rate of instrumental vaginal delivery and longer labors, particularly in nulliparous women. Women receiving epidural are also more likely to have intrapartum fever and their infants are more likely to be evaluated and treated for suspected sepsis. There is insufficient evidence to determine whether epidural does or does not tend to increase the risk of cesarean delivery or fetal malposition. Adverse effects on the fetus may occur in the subset of women who are febrile.

Women should be informed of unintended effects of epidural clearly supported by the evidence, especially since epidural use is almost always an elective procedure. Further research is needed to advance our understanding of the unintended effects of epidural. Improved information would permit women to make truly informed decisions about the use of pain relief during labor. (Am J Obstet Gynecol 2002;186:S31-68.)

Key words: Epidural, labor, analgesia, combined spinal epidural, neonate, fetus, fever, temperature, cesarean section, instrumental vaginal delivery, fetal malposition, perineal lacerations, sepsis evaluation, bilirubin, seizures, hypotonia, Apgar scores

Epidural analgesia provides the most effective labor pain relief currently available and its use has increased dramatically in the last 20 years. More than half of women delivering babies, or approximately 2 million women each year, receive epidural for pain relief during labor.[1]

Epidural analgesia, like almost all medical treatments, has been associated with a number of unintended effects. Reports have linked epidural with a variety of adverse effects during labor, including higher rates of cesarean delivery, instrumental vaginal delivery, fetal malposition, and intrapartum fever; it has also been associated with longer labors. Adverse neonatal outcomes have also been reported, including jaundice and differences in behavioral testing. Although the data on several unintended effects of epidural use for labor pain are consistent, information regarding a number of possible effects is inconclusive. Therefore, despite considerable research, there remains no clear consensus on unintended maternal and neonatal side effects that result from the use of epidural analgesia during labor.

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Choosing an epidural for intrapartum pain relief is almost always elective: the decision rests with the laboring woman and her provider. Thus, it is critical that both understand the potential risks as well as the benefits that accompany its use. We review the literature related to unintended effects of epidural and combined-spinal epidural techniques used to produce pain relief during labor in low-risk women.

Methods

Identification of studies

Search strategy. A literature search was carried out in August 2000 and updated in May 2001. MEDLINE, PreMEDLINE and Current Contents/Clinical Medicine were searched using the following terms as medical subject headings and text words: analgesia, epidural; anesthesia, epidural; anaesthesia, epidural; analgesia, obstetrical; anesthesia, obstetrical; anaesthesia, obstetrical; delivery; intrapartum; labour; labor; birth; labor stage, first; labor stage, second; labor stage, third; labor complications; labor, induced; trial of labor. Articles were limited to English language studies. If foreign language studies differ in their outcome, this could have influenced our results. Editorials, comments, letters, historic articles, and case reports were excluded from the search. In addition, a search of randomized trials in the Cochrane Library Specialized Register of the Pregnancy and Childbirth Group (SR-PREG) was obtained. All of the nearly 1900 articles from this search were reviewed and potentially relevant articles obtained for more detailed review. Bibliographies of included articles and review articles were examined to identify additional articles.

Criteria for study inclusion and exclusion. We limited our review to original reports in peer review journals since 1980, except when they measured neonatal outcomes, where we have included articles back to 1970 because there is a dearth of material available in this area. Abstracts were excluded because they are not uniformly identifiable by database searches and therefore, complete and unbiased ascertainment is not possible. In addition, there are inadequate data in abstracts to assess the validity of study results. We elected not to contact authors for further information because of the short time frame for preparation of the review. We included both randomized trials and observational studies and excluded the following categories of studies:

1. *Studies with no control group (case series)*
2. *Studies that evaluate specific drug regimens*
3. *Studies that examine epidurals administered to produce anesthesia for cesarean delivery*
4. *Studies that examine outcomes only for the overall population of delivering women.* These are primarily studies that present outcomes in the overall population before and after introduction of an on-demand epidural service that have been referred to as "natural experiments."[2] These studies do not provide a meaningful evaluation of the effects of epidural during labor because they do not distinguish laboring from nonlaboring women. To demonstrate the reason why these studies are not informative, we examined data on cesarean delivery for all births at Brigham and Women's Hospital during 1998. In that year, the hospital performed 9089 deliveries, and 65% of women (n = 5883) received epidural for pain relief during labor. We found that the rate of cesarean delivery among women who received epidural for pain relief was 11% (657/5883), much lower than the 39% (1248/3206) cesarean delivery rate for women who did not receive epidural. This means that 66% of cesarean deliveries (1248/1905) occurred among women who did not receive epidural for pain relief. However, most women with cesarean delivery but no epidural (89% or 1105/1248) were never in labor, either because of a medical/obstetric condition or because a repeat cesarean delivery was elected. Because a majority of cesarean deliveries occurred in women who could not choose epidural for relief of labor pain (because they were never in labor), any increases in cesarean deliveries among laboring women would be diluted and very difficult to discern in studies that include the overall population. In the scenario described above, a doubling of the cesarean delivery rate among low-risk nulliparous women with spontaneous labor (the subgroup where an effect of epidural has been most often suggested), would increase the overall cesarean delivery rate in our institution by slightly less than 2% (from 21.0% to 22.9%). A study population of approximately 7500 women in each period would be required to have 80% power to detect a difference of this magnitude.
5. *Studies conducted exclusively in high-risk populations because our review focuses on low-risk women.*
6. *Studies where population selection renders results uninformative.* Studies where criteria for inclusion were based on labor outcome (eg, limited to women with spontaneous vaginal deliveries or to women who had an uncomplicated labor course)[3,4] are not useful for evaluation of labor outcomes and were excluded from our consideration of them. For example, should a study find that for women with spontaneous vaginal deliveries, the length of labor was the same for women with and without epidural, there would be several possible explanations for those results. One explanation would be that epidural does not influence the length of labor. It is also possible, however, that these findings resulted because long labors (whether with or without epidural) are interrupted by either cesarean or instrumental vaginal deliveries. This interruption could happen in the epidural group either more often (if epidurals make labor longer) or less often (if epidurals shorten labor), but we would not know if that was the case since women with cesarean or instrumental vaginal delivery would have been excluded from the

study. The inability to distinguish between these explanations makes such studies uninformative.

7. *Studies with analytic choices that make results impossible to interpret.* When studies examine the association of epidural with length of labor or cesarean delivery separately for women who received and did not receive oxytocin. It is not possible to evaluate the effects of epidural. Women treated with oxytocin already have failure to progress (since this is the reason they were treated) and would be expected to have a higher rate of long labor and cesarean regardless of whether their failure to progress was because of epidural (if epidural slows labor) or some other cause. An analysis that examines these 2 groups separately misses the real question, which is, do women with epidural end up in the oxytocin ("failure to progress") group more often? Therefore, these studies were excluded if data from the 2 groups could not be recombined.

Assessment of study quality and validity. All papers were reviewed with regard to methods, including strengths of the designs and analyses. No formal scoring system was used. Observational studies and randomized trials were considered. The relative weight accorded to a specific study was determined by its overall methodologic quality. The rationale for these choices is discussed below.

Study type: randomized trials and observational studies. Randomized controlled trials (RCTs) have generally been considered to represent the "gold standard" because subjects in the study arms are most often equivalent for both measured and unmeasured characteristics. There has been much debate related to the role of observational studies in clinical research. Observational studies have often been viewed as subject to bias because of unrecognized confounders and therefore prone to give different, less accurate results. Recently, 2 articles in The New England Journal of Medicine[5,6] have called this assumption into question. Both articles note that the view of observational studies as unreliable has been based largely on evaluations of studies conducted in the 1960s and 1970s, in which results of studies using historical controls were compared with results of randomized trials. In contrast, the analyses by Concato et al[5] and Benson et al[6] compare the results of randomized trials with the results of observational studies conducted using more current methods (cohort studies with concurrent controls and case control studies). Both evaluations found that the results of RCTs and observational studies were remarkably similar for the broad range of clinical treatments they examined. Assessment of quality is complex and cannot be assigned based solely on a determination of study design. While randomized trials represent a strong study design with many important advantages, randomization does not guarantee methodologic excellence or valid results. Both randomized trials and observational studies may be well done or poorly done. We therefore have included both randomized and observational studies and individually assessed the quality of each study in terms of design and analysis, rather than based on design category.

Protocol noncompliance (crossover) and interpretation of randomized trials. The proportion of women who do not receive the treatment to which they were assigned (women in the epidural group who do not receive epidural and women in the no epidural or opioid group who do receive epidural) has important effects on the results of randomized trials. When such crossover occurs, the proportion of women in each group who receive epidural becomes more similar, making the expected difference in outcome between the groups smaller. Fig 1 illustrates the effect of crossover in a theoretical randomized trial in which epidural is truly associated with a doubling of the cesarean delivery rate (20% with epidural and 10% without epidural). If in this theoretical study, 30% of women in each randomized group do not receive the treatment to which they were assigned, the expected rates in the intention-to-treat analysis become 13% in the no epidural group and 17% in the epidural group. This smaller difference is much harder to detect. A study of 400 women would have 80% power to find the difference between 10% and 20%, whereas a study of 2500 women would be needed to have similar power in a study where the expected rates were 13% and 17%.

The 30% rate of crossover used in this example is similar to that found in many of the randomized trials of epidural, including all of the large studies (Table I). When so many women do not receive their assigned treatment, the proportion receiving epidural in each group becomes more similar and the intention-to-treat analysis, though technically correct, is difficult to interpret.

Formal scoring systems. At least 25 scales exist for evaluating the quality of randomized trials with wide variability in the factors included. Use of these scores is controversial,[7] in part because it introduces a subjective element into the analysis. A recent publication in *The Journal of the American Medical Association*[8] concluded that use of summary scores to identify trials of high quality is problematic since the particular one chosen can dramatically influence the inferences drawn from meta-analyses. Although the concept of scoring systems is appealing, the complexities of study design and analysis make it difficult (and perhaps impossible) to assess quality based on a small number of questions with categoric responses. We therefore elected not to use a formal scoring system in our evaluation.

Studies and analyses that were accorded less weight. We believe that the following analytic elements hamper interpretability of data. Therefore, we gave studies with these analytic elements less weight in reaching our conclusions:

1. *Studies with nonconcurrent (historical) controls*, because these studies are often regarded as providing less reliable evidence about treatment even when they are done well.[9] In a comparison of the results of randomized trials of treatments with studies using historical controls,

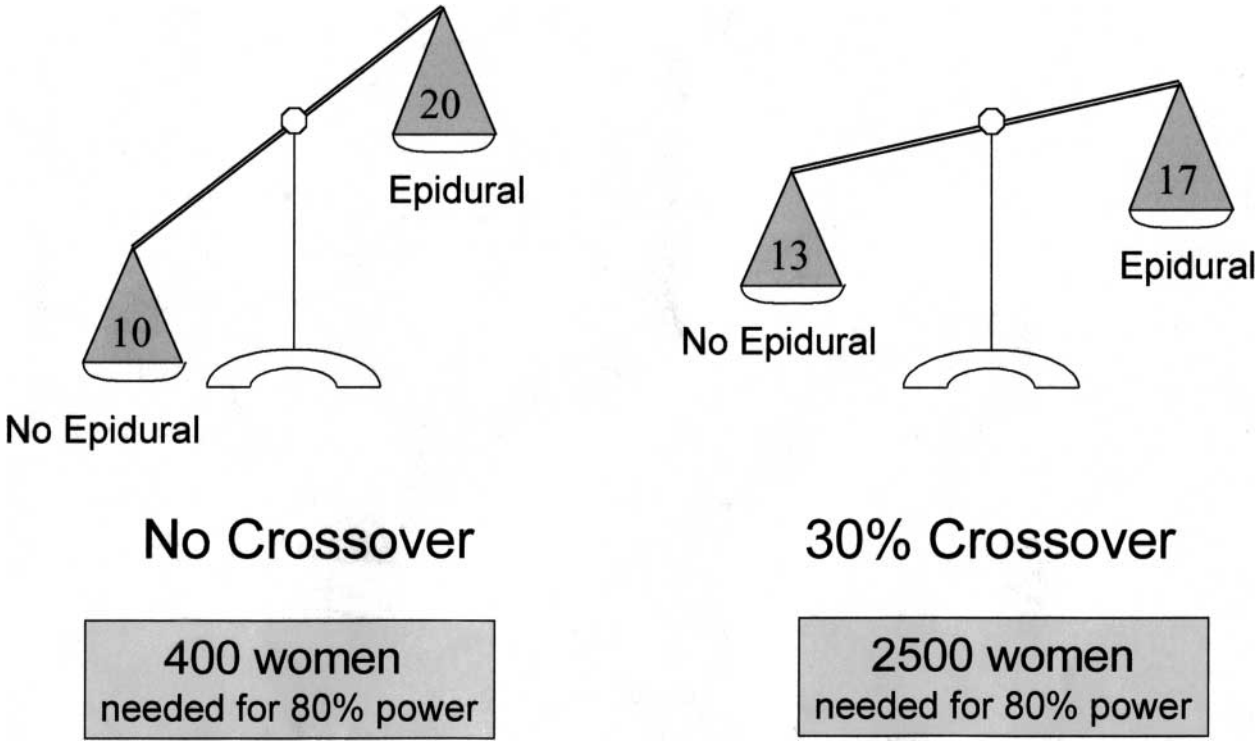

Fig 1. Effect of crossover on expected rates and study power in randomized trials of epidural analgesia.

Table I. Rates of crossover in randomized trials of epidural and labor outcome

Study	*No. of subjects*	*Crossover (%)* *No epidural*	*Epidural*
Larger studies			
Ramin et al[19]	869	34	35
Sharma et al[18]	715	1	32
Clark et al[20]	318	52	6
Loughnan et al[21]	614	56	15
Howell et al[15]	369	28	33
Smaller studies			
Philipsen and Jensen[31]	111	—	—
Thorp et al[17]	93	0	2
Bofill et al[30]	100	24	4
Nikkola et al[29]	20	40	—

Sacks et al[10] found vastly differing results for the same outcomes of interest.

Several types of problems may arise in these studies. First, there could be changes in the population served by an institution or changes in practice over time. Results may also be influenced by secular trends in outcome in the environment. For example, between 1986 and 1996, the cesarean delivery rate in the United States decreased by 16% (from 24.7% to 20.7%). Any intervention introduced to lower the cesarean delivery rate implemented during that period was likely to succeed, and new treatments introduced (such as epidural) would be less likely to appear to increase the rate of cesarean delivery.

In addition, most labor care providers are aware of the purported association between epidural and cesarean delivery, and this awareness may affect their clinical decision making. When an epidural service is introduced, this awareness could consciously or unconsciously result in changes in clinical behavior that have an impact on the cesarean rate. In fact, attention to the cesarean delivery rate (for example, by informing clinicians about their rates) is considered an important element of programs attempting to decrease cesarean delivery rates.[11,12]

2. *Studies that fail to distinguish sub-populations in which patterns of labor and the effects of epidural may differ.* Patterns of labor and risk of cesarean delivery differ substantially across subpopulations of women. Nulliparous women tend to have longer labors,[13] are more likely to have a cesarean delivery,[14] and are also more likely to request epidural analgesia.[15] The same is true for women whose labors are induced.[16] Substantial confounding may occur if differences between these subgroups are not taken into account by limitation of the population studied or by control in multivariate analyses. In addition, it is important to consider that the effect of epidural may differ between subgroups.

3. *Exclusion of specific analyses within studies.* Some studies we included had one or more specific analyses that could not be clearly interpreted and were excluded from consideration. For example, we excluded analyses evaluating the association of epidural with length of labor or cesarean delivery in which oxytocin use was included

in the multivariate analyses. When investigators control for oxytocin in this way, they are trying to take into account the possibility that women with slower labors may be more likely to request an epidural. However, controlling for oxytocin use is not the best way to take those differences in labor characteristics into account because it may lead to incorrect conclusions. If epidural causes slow labor or failure to progress, then the need for oxytocin may result directly from epidural use. Longer labors and cesarean deliveries are other consequences of failure to progress. Because controlling for oxytocin use makes it impossible to investigate whether epidural contributed to the occurrence of the failure to progress, we excluded those analyses from consideration. We believe that a better approach to taking into account differences between women who choose and do not choose epidural is to control for the baseline characteristics of women's labors including cervical dilation and station at admission and the early rate of cervical dilation (before administration of epidural or oxytocin). We therefore relied on studies that used this approach.

Presentation of results

Data synthesis and presentation. Details of the studies we reviewed are provided in tables organized by outcome. No formal synthesis of the data was performed. All observational studies were assessed regarding the presence of confounding. The degree of crossover in randomized trials was noted. We re-analyzed some of the data presented in the published papers to eliminate methodologic difficulties (such as stratification by oxytocin). Whenever possible, we present separate data for nulliparous and multiparous women rather than combined data. In addition, we calculated relative risks (RRs) and confidence intervals (CIs) for studies when they were not presented.

Results

Cesarean delivery outcomes. Although many studies have reported an association of epidural with cesarean delivery, there is disagreement about whether epidural causes cesarean delivery or whether the appearance of an association results from differences between women who choose or do not choose epidural. There is agreement, however, that whatever the reason for the association, it involves cesarean deliveries for failure to progress (dystocia), not those for nonreassuring fetal status. None of the 5 RCTs[17-21] and 7 observational studies[16, 22-27] that examined the indication for cesarean delivery found a significantly higher cesarean delivery rate for nonreassuring fetal testing. Because dystocia is responsible for most cesarean deliveries in low-risk populations, we will not present specific data related to indication, but will concentrate our evaluation on the broader question of whether epidural causes cesarean deliveries.

Randomized controlled trials. Our search identified ten RCTs that examined the association of epidural analgesia with cesarean delivery (Table II),[15, 17-21, 28-31] Five of the trials were conducted in the United States, 2 in England, and 1 each in Wales, Finland, and Denmark. The association of epidural with cesarean delivery varies dramatically within these trials with RRs ranging from 0.7 to 11.2.

Seven RCTs were conducted in women with term singleton pregnancies, a vertex fetus, and spontaneous onset of labor,[17, 18, 20, 29, 30] whereas 2 others had similar criteria except for the inclusion of women who were induced as well as those with spontaneous labor.[15, 21] Eight of the 10 trials were either conducted solely in nulliparous women or present at least some results separately for nulliparous and multiparous women.[15, 17, 18, 20, 21, 28-30] The earliest study, Robinson et al,[28] randomized 386 low-risk women late in pregnancy but limited the analysis to the 93 women who completed a series of interviews and received only the analgesic allotted to them. Because only one quarter of the women randomized were included in the analysis, and those included were not an unbiased sample, this study should not be interpreted as an RCT. Also, it appears that women with cesarean deliveries were excluded because none are reported.

Several other relatively small RCTs have been conducted with varying results. Philipsen and Jensen[31] conducted a trial of 111 women (93% nulliparous) in which epidural was discontinued after 8-cm dilation. Although they reported a 60% higher rate of cesarean delivery among women receiving epidural analgesia (18% vs 11%), this difference was not statistically significant. A study enrolling 800 women would be needed to have 80% power to detect a difference of this magnitude.

Bofill et al,[30] in a study of 100 women, found a similar 70% increase in the rate of cesarean delivery (10% vs 6%) that was also not statistically significant. Other important factors influencing the interpretation of this study are that 24% of women in the control group received epidural and that the mean birth weight in the epidural group was 175 g lower than in the no-epidural group. Since higher birth weight is associated with an increase in the rate of cesarean delivery, all other things being equal, a lower rate of cesarean delivery might be expected in the epidural group. This difference should have been controlled in the analysis.

A third small trial was performed by Thorp et al,[17] who randomized 93 term nulliparous women in spontaneous labor. Only one woman in the no-epidural group received an epidural. These authors reported an 11-fold increase in the cesarean delivery rate in the epidural group and stopped the trial early based on this finding. Finally, Nikkola et al[29] conducted a very small study of 20 women in which no cesarean deliveries were reported in either group.

The 5 remaining RCTs, Ramin et al,[19] Sharma et al,[18] Clark et al,[20] Loughnan et al,[21] and Howell et al[15] are larger but all have a high proportion of women who did not receive the treatment to which they were assigned

Table II. Method of delivery in randomized trials comparing epidural and opioid analgesia

Author (y)	*#/Group Epidural/ Control*	*Bupivacaine conc. ± opioid (O); Intermittent (I)/ Continuous (C)*	*Epidural stopped/ decreased in 2nd stage*	*Intent-to-treat analysis*	*% Epidural group not receiving epidural*	*% Control group receiving epidural*	*% Instrumental deliveries*		
							Epidural	*Controls*	*RR (95% CI)*
Nulliparas									
Robinson et al[28] (1980)	28/30	.5% (I)	N	N*	—	—	61	27	2.3 (1.2, 4.4)
Thorp et al[17] (1993)	48/45	.125% (C)	N	Y	2	0	19	11	1.7 (.6, 4.7)
Bofill et al[30] (1997)	49/51	.125% + O (C)	N	Y	4	24	80	55	1.5 (1.1, 1.9)
Nikkola et al [29] (1997)	10/10	.5% (I)	Y	Y	—	40	40	0	—
Sharma et al[18] (1997)	197/189	.125% + O (C)	Y‡	Y	32§	1§	—	—	—
Clark et al[20] (1998)	156/162	.125% + O (C)	N	Y	6	52	15	12	1.3 (.8, 2.2)
Loughnan et al[21] (2000)	304/310	.125% (C)	Y	Y	15	56	29	26	1.1 (.9, 1.4)
Howell et al (2001)[15]	184/185	.25% (I)	N	Y	33	28	30	19	1.5 (1.1, 2.2)
Multiparas									
Robinson et al[28] (1980)	17/18	.5% (I)	N	N*	—	—	29	6	5.3 (.7, 40.8)
Sharma et al[18] (1997)	161/168	.125% + O (C)	Y‡	Y	32§	1§	—	—	—
Mixed Parity									
Philipsen and Jensen[31] (1989)	57/54	.375% (I)	Y‖	Y	—	—	25	26	1.0 (.5, 1.8)
Ramin et al[19] (1995)	432/437	.125% + O (C)	Y‡	N*	35	34	9	3	3.2 (1.7, 5.9)
Sharma et al[18] (1997)	358/357	.125% + O (C)	Y‡	Y	32	1	7	4	1.7 (.9, 3.2)

*Analysis of protocol compliant patients only.
†Unclear if study results exclude those with cesarean delivery.
‡Epidural decreased or stopped in 2nd stage if progress inadequate.
§Estimate of crossover combines nulliparous and multiparous subjects.
‖No epidural boluses after 8-cm dilatation.

Table III. Maternal and fetal outcome according to randomization group and treatment received in the trial of Clark et al[20]

	Randomized to epidural		*Randomized to opioid*	
	Received epidural	*Received opioid*	*Received opioid*	*Received epidural*
No. of women	147	9	78	84
Cesarean for dystocia, n (%)	8 (5.4)	1*	3 (3.8)	14 (16.6)
Apgar score <7 at 1 min, n (%)	19 (12.2)	2*	8 (10.3)	21 (25.0)
Apgar score <7 at 5 min, n (%)	4 (2.6)	0*	1 (1.3)	7 (8.3)

*Number of patients too small for valid estimation of rates.
From Lieberman E, Lang JM, Frigoletto F, Cohen A. Epidurals and cesareans: The jury is still out. Birth 1999;26(3):196-8. Reprinted by permission of Blackwell Science, Inc.

(Table I). For example, in 2 of the large studies, more than half of the women assigned to receive only opioid actually received epidural. As we discussed in the Methods section (Assessment of quality and validity, Fig 1), this crossover makes the proportion of women in each group who receive epidural more similar. Since the expected difference in outcome between the groups is decreased, a finding of no difference is difficult to interpret.

Clark et al[20] reports specific information about outcomes in women who did and did not receive their assigned treatment, allowing an evaluation of the effect of crossover on outcome. This study reported no difference in the cesarean delivery rate for the groups randomized to opioid and epidural. However, more than half of the women (84/162) assigned to receive only opioid actually received epidural analgesia and, strikingly, almost all of the cesarean deliveries for dystocia in the group assigned to receive opioid (14 of 17) occurred in women who actually received epidurals (Table III). In the intention-to-treat analysis (all women analyzed according to original group assignment regardless of the type of pain relief they actually received), these 14 cesarean deliveries are counted in the opioid group, increasing the cesarean rate for that group. When such a high proportion of subjects do not get the treatment to which they were assigned, the intention-to-treat analysis, though technically correct, is impossible to interpret.[32, 33]

There are other unusual aspects to the findings of Clark et al[20] For example, if epidurals have no effect on the likelihood of cesarean delivery, the overall rate of cesarean deliveries for dystocia in the 2 randomly assigned groups should have been similar. Instead, the rate was nearly twice as high in the group assigned to opioid treatment (10.5% versus 5.8%). The increased rate of cesarean deliveries in the opioid group was because of the very high rate (16.6%) among the subgroup that crossed over to receive epidural (Table III). The substantial difference in overall rates suggests that either the 2 groups were, by chance, different at randomization, or that there were important differences in obstetric practice between the two groups, especially in the subgroup of women who were assigned to opioids but received epidurals. This concern is heightened by differences in infant outcome for that

% Cesarean deliveries			% Spontaneous vaginal delivery		
Epidural	*Controls*	*RR (95% CI)*	*Epidural*	*Controls*	*P value*
	Not reported†		—	—	—
25	2	11.2 (1.5, 83.1)	56	87	.001
10	6	1.7 (.4, 6.9)	10	39	.001
0	0	—	60	100	.1
5	6	0.8 (.3, 1.9)	—	—	—
10	14	0.7 (.4, 1.3)	75	74	.9
12	13	0.9 (.6, 1.4)	59	61	.9
7	9	0.8 (.4, 1.7)	63	72	.07
	Not reported†		—	—	—
3	3	.8 (.2, 3.1)	—	—	—
18	11	1.6 (.6, 4.1)	57	63	.6
9	4	2.3 (1.3, 4.0)	82	93	<.0001
4	5	.8 (.4, 1.7)	89	91	.4

group. In particular, infants of women who were assigned to opioids but received epidurals were far more likely to have Apgar scores <7 at both 1 minute (25.0%) and 5 minutes (8.3%), compared with either infants of women who were assigned to and received epidurals (12.2% at 1 minute, 2.6% at 5 minutes) or infants of women who were assigned to and received opioid (10.3% at 1 minute, 1.3% at 5 minutes). These findings reinforce the concern that the 2 groups were inherently different or that the treatment they received was different.[32] Concerns related to group comparability, in addition to the concerns related to crossover, severely limit the ability of this study to inform us about epidural and cesarean delivery.

Another problem in interpretation arises in Ramin et al,[19] who randomized 1330 nulliparous and multiparous women, but include in the analysis only women receiving the treatment to which they were assigned. Based on that analysis, the authors conclude that epidural is associated with a 2-fold increase in cesarean delivery. However, this may not be the case because approximately 35% of women in each group did not receive the treatment to which they were randomized. The analysis of only protocol-compliant women (65% of the randomized population) negates the benefits of randomization and introduces differences between the groups that must be controlled in the analysis. This is particularly significant because the women who accepted their assigned treatment differed in the epidural and no-epidural groups. In the epidural group, nulliparous women were more likely to accept the assigned treatment and to be included in the analysis. In contrast, in the opioid group, multiparous women were more likely to accept the assigned treatment. This imbalance results in the expectation of a higher cesarean delivery rate in the epidural group (because nulliparas have a higher cesarean delivery rate) and failure to control this confounding factor makes the results impossible to interpret.

There are also concerns about the generalizability of the results of these trials to the general population of childbearing women. For several studies, the women enrolled were much younger, on average, than most women giving birth in this country, which may be important because the rate of cesarean delivery increases with maternal age.[34] In Ramin et al,[19] 34% of women enrolled were ≤19 years old; in Sharma et al,[18] the average age was approximately 22 years, and in Clark et al,[20] 55% of enrollees were ≤18 years old. In contrast, in 1997, only 8% of women giving birth in the United States were ≤18 years old.[35] In addition, the 3 studies reporting reasons for protocol-noncompliance, all noted that rapid delivery was an important contributor to failure of women to receive analgesia.[15, 18, 19] In Sharma et al, 20% of women in each randomized group delivered too rapidly to receive either epidural or parenteral analgesia. Although less detailed information is provided by Ramin et al (conducted in the same institution), the proportion appears similar. Howell et al[15] also noted that noncompliance in the epidural group (33%) was usually because of rapid progress of labor. This very high proportion of rapid deliveries suggests that the populations enrolled in these studies may be a distinct subgroup not typical of most women delivering. The high rate of rapid delivery may reflect the fact that these studies included only women who, when approached during labor, were willing to have their method of pain relief determined by randomization.

Observational studies with concurrent controls. Of the 33 observational studies that met the inclusion criteria for our review, 18 were conducted in the United States, 8 in England, 2 each in Finland and Israel, and 1 each in Belgium, Ireland, and Pakistan.[16, 23-27, 36-61] These studies were classified by 3 factors that predict cesarean delivery and represent major potential confounders of the association of epidural with cesarean delivery, and these are (1) parity of the study population, (2) whether the study included women in spontaneous labor, induced labor, or both, and (3) whether the study was limited to low-risk women, defined for this analysis as women at term, with singleton, vertex fetuses and no previous cesarean deliveries. Findings in these studies are presented in Table IV. The method of pain relief in the no-epidural group is not shown in this table because it was often not uniform within the group and for many studies no information was provided.

There is substantial variation in the association of epidural with cesarean delivery in these studies. Even

Table IV. Observational studies that compare method of delivery for women with and without epidural: Studies that included all women in the population

Author (y)	*#/Group Epidural/ No epidural*	*Bupivacaine conc. ± Opioid (O); Intermittent (I) or Continuous (C)*	*All subjects low-risk**	*Inductions excluded*	*% Instrumental deliveries*		
					Epidural	*No epidural*	*RR (95%CI)*
Nulliparas							
Studd et al[38] (1980)	183/650	—†	Y	Y	60	20	3.0 (2.5, 3.7)
Kanto et al[36] (1983) (I) ‡	100/100	.5%(I)§	N	N	13	4	3.3 (1.1, 9.6)
(II)	50/50	.5%(I) §	N	N	16	6	2.7 (.8, 9.5)
Harrison et al[37] (1987)	50/20	.375% (I)	N	N	62	35	1.8 (.9, 3.3)
Muhlen-Schulte and Wade[39] (1988)	74/46	—	N	N	50	13	3.8 (1.8, 8.4)
Neuhoff et al[40] (1989)	256/254	—	Y	N	17	12	1.5 (1.0, 2.2)
Thorp et al[26] (1989)	447/264	.125% (C)	Y	Y	—	—	—
Manyonda (I) ‖	200/200	—§	Y	Y	43	13	3.3 (2.2, 4.9)
et al[41] (1990) (II) ¶	200/200	—	Y	Y	50	33	1.5 (1.2, 1.9)
Thorp et al[27] (1991)	294/206	.125% (C)	Y	Y	24	7	3.6 (2.1, 6.2)
Kong et al[43] (1992)	93/257	.25% (C)	Y	Y	52	19	2.4 (1.8, 3.2)
Peaceman et al[42] (1993)	504/196	—	Y	Y	—	—	—
Stoddard et al[44] (1994)	78/40	.0625% or .125% + O (C)	Y	Y	47	20	2.4 (1.2, 4.6)
Driver et al[45] (1996)	2038/2324	.25%(I) or .125% + O (C)	Y	N	—	—	—
Hemminki and Gissler [46] (1996)	7021/16,699	—	N	N	12	9	1.3 (1.2, 1.4)
Lieberman et al[23] (1996)	991/742	.125% + O (C)	Y	Y	19	4	4.8(3.3, 7.1)
Lyon et al[24] (1997)	247/174	Variable	Y	N	32	16	2.0 (1.4, 3.0)
Thompson et al[47] (1998)	406/235	Variable (C or I)	Y	Y	17	9	1.9 (1.2, 3.0)
Seyb et al[48] (1999)	1286/271	.125% + O (C)	Y	N	—	—	—
Walker et al[49] (1999)	65/168	—	Y	Y	26	7	3.7 (1.9, 7.2)
Yancey et al[51] (1999)	1728/625	.0625% or .125% (C)	N	N	19	10	1.9 (1.5, 2.5)
Traynor et al[52] (2000)	860/277	.0625% or .125% (C)	Y	N	—	—	—
Zimmer et al[50] (2000)	223/151	.25% + O (I)	Y	N	22	13	1.7 (1.0, 2.7)
Beilin et al[199] (2000)	1139/89	.125% or .0625% + O (C)	Y	N	—	—	—
Multiparas							
Studd et al[38] (1980)	99/1023	—	N	Y	24	6	3.8 (2.5, 5.8)
Hemminki and Gissler[46] (1996)	1847/31,751	—	N	N	6	2	3.7 (3.0, 4.5)
McRae-Bergeron et al[53] (1998)	100/102	.11 or .125% + O(C,I)#	N	N	9	2	4.6(1.0, 20.7)
Zimmer et al[50] (2000)	141/322	.25% + O (I)	N	N	10	2	5.3 (2.1, 13.6)
Mixed Parity							
Kanto et al[36] (1983)	102/101	.5% (I)§	N	N	11	4	2.7 (0.9, 8.3)
Diro and Beydoun[54] (1985)	43/43	.25% (I)	N	Y	26	9	2.8 (1.0, 8.0)
Niehaus et al[56] (1988)	110/514	Variable drug	N	N	24	4	6.8 (3.8, 11.9)
Bright[55](1993)	100/100	–	N	N	37	13	2.9(1.6, 5.0)
Khan et al[57](1993)	64/118	.25% or .5%	N	N	50	24	2.1(1.4, 3.2)
Cammu et al[16](1994)	297/703	.125% to .2% + O(I)	N	N	24	16	1.6(1.2, 2.5)
Newton et al[106](1995)	62/124	.125%+O(C)	N	N	15	2	9.0(2.0, 40.4)
Russell and Reynolds[129](1996)	319/131	(.0625% or .125%)+O(C)	N	N	37	10	3.8(2.2, 6.4)
Rojansky et al[25](1997)	112/98	.25%(I)	N	N††	26	4	6.3(2.3, 17.4)
Okojie and Cook[60](1999)	81/41	.25%(I)	N	N	35	15	2.4(1.1, 5.3)
Sudain et al[61](1999)	494/178	.125%+O(C) ‡ ‡	N	N	76	17	4.4(3.2, 6.0)

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Information regarding epidural not provided. ‡Historical control group. §Epidural stopped in second stage. ‖Analysis I: 1983 study. ¶Analysis II: 1985 study. #Patient-controlled analgesia for intermittent administration. **Primary cesarean delivery date. ††Inductions only. ‡‡About 50% of subjects received 5 to 10 mL of 1% lidocaine just before delivery.

among the relatively homogenous group of 10 studies conducted in low-risk nulliparas in spontaneous labor,[23, 26, 27, 38, 41-44, 47, 49] RRs vary from 1.6 to 6.5. The reasons for the variation are difficult to interpret and could relate to differences in populations, patterns of epidural use and management styles. The main issue in

% Cesarean deliveries			% Spontaneous vaginal deliveries		
Epidural	*No epidural*	*RR (95% CI)*	*Epidural*	*No epidural*	*p-value*
4	2	1.6 (0.7, 3.6)	36	78	< .0001
5	4	1.3 (0.4, 4.5)	82	92	.04
0	0	—	84	94	.1
6	0	—	32	65	.01
35	7	5.4 (1.7, 16.8)	15	80	< .0001
19	9	2.1 (1.4, 3.2)	64	79	< .0001
12	6	2.2 (1.3, 3.8)	—	—	—
18	4	4.5 (2.2, 9.4)	39	83	< .0001
19	4	4.8 (2.3, 9.9)	31	63	< .0001
14	5	2.9 (1.5, 5.7)	62	88	< .0001
15	2	6.5 (2.6, 16.3)	33	79	< .0001
15	4	4.3 (2.0, 9.2)	—	—	—
9	5	1.8 (0.4, 8.2)	44	75	.001
18	13	1.3 (1.2, 1.5)	—	—	—
14	12	1.2 (1.1, 1.2)	74	79	< .0001
17	4	4.3 (3.1, 6.0)	64	92	< .0001
14	4	3.5 (1.6, 7.8)	54	80	< .0001
14	2	6.4 (2.6, 15.6)	69	89	< .0001
12	3	3.7 (1.9, 7.1)	—	—	—
34	9	3.8 (2.1, 6.8)	40	84	< .0001
19	11	1.7 (1.3, 2.2)	62	79	< .0001
14	3	4.2 (2.2, 8.1)	—	—	—
10	4	2.5 (1.0, 6.0)	68	83	.0006
15	8	1.9 (0.9, 3.9)	—	—	—
4	1	3.8 (1.2, 11.6)	72	93	< .0001
16	5	3.4 (3.1, 3.9)	78	93	< .0001
5	0	—	86	98	.002
8	3	2.5 (1.1, 5.8)	82	95	< .0001
5	4	1.2 (.3, 4.5)	84	92	.09
16	0	—	58	91	.0005
13	2	6.0 (2.8, 12.8)	63	94	< .0001
11**	12**	0.9(.4, 2.0)	52	75	.0007
9	16	0.6(.2, 1.4)	41	60	.01
8	2	3.6(1.9, 6.6)	68	82	<.0001
5	0	—	80	98	<.0001
14	0	—	49	90	<.0001
11	6	1.8(.7, 4.5)	63	85	<.0001
25	15	1.7(.7, 3.9)	40	70	.002
5	17	0.3(.2, 0.5)	19	66	<.0001

the interpretation of these observational studies is self-selection, that women who choose epidural are different from those who do not. Women who select epidural are more likely to be slightly shorter, to have larger infants and to be further along in gestation.[23, 62] Perhaps more important, women who go on to choose epidural are admitted to the hospital earlier in labor[23, 62] and dilate more slowly just after admission compared with women who do not go on to receive epidural.[23] The rate of epidural use has been noted to decrease directly with greater cervical dilation at admission.[16] Few observational studies take these differences into account.

We identified only 3 studies that controlled for differences in labor characteristics. In a study of 711 term, nulliparous women in spontaneous labor, Thorp et al[26] found that the association of epidural analgesia with cesarean delivery for dystocia remained significant when controlling for centimeters dilation at admission (among other factors) in a logistic regression analysis. In a second study, Thorp et al[27] controlled even more carefully for labor characteristics by categorizing women by their rate of dilation in early labor (< 1 cm/hour or ≥1 cm/hour). Although dilating quickly was associated with a lower rate of cesarean delivery, the association of epidural with cesarean delivery was present for both slow dilators (22% epidural, 7% no-epidural) and fast dilators (9% epidural, 3% no-epidural).

In the third study, Lieberman et al[23] evaluated 1733 term, low-risk women with spontaneous onset of labor. They reported a cesarean delivery rate of 4% for women without epidural and 17% for women with epidural. To adjust for the differences between women who chose and did not choose epidural, the authors used statistical methods (propensity scores) to place women into 5 groups based on characteristics that differ for women receiving and not receiving epidural. Characteristics taken into account in forming the groups included pregnancy and labor factors (dilation at admission, station of the fetal head at admission, rate of cervical dilation early in labor, gestational age and infant birth weight), and maternal characteristics that predict epidural use (weight, height, and race). Women in group 1 came in earliest in labor (1.9 cm on average) and were dilating most slowly (.16 cm/hour on average). Many women in this group went on to choose an epidural but all women in group 1 had these labor characteristics whether or not they went on to receive an epidural. Similarly, women in group 5 came with their labor most advanced (5.2 cm on average) and were dilating the most rapidly (1.9 cm/hour on average). Fewer of these women chose epidural, but late admission and rapid progression were present among all women in group 5, women who went on to have an epidural and women who did not. In all 5 groups, the cesarean delivery rate was higher among women who received epidural, suggesting that the association was present regardless of the characteristics of a woman's labor. In a logistic regression analysis controlling for these factors, epidural was associated with a 3.7-fold increase in the rate of cesarean delivery (95% CI, 2.4, 5.7).

Studies with historical controls. Three studies examined cesarean delivery rates among laboring women before and after introduction of an epidural service or during a time of rapid change in epidural use.[24, 63, 64] All show little or no increase in cesarean delivery rates between the periods. However, as noted in the Methods section, changes in practice, secular trends, and awareness by the provider of the possible association all limit the ability of these studies to contribute to our understanding.

Summary: Cesarean delivery. Although many studies have noted an association of epidural analgesia with cesarean delivery, the question of whether epidural causes cesarean delivery has remained controversial. The crux of the debate is whether the difference in cesarean delivery rates observed is because of the epidural itself or other differences between women who receive epidural analgesia and women who do not. In other words, are the women who receive epidurals having the hardest labors, and would they be at higher risk for cesarean delivery even if they did not receive an epidural?

The data currently available do not provide an answer to these questions. Existing randomized trials are either too small or do not allow clear interpretation of the data. For example, Thorp et al[17] conducted a study that found an association between epidural and cesarean deliveries but was too small to allow definitive conclusions. Unfortunately, all 5 large studies[15, 18-21] have major problems related to protocol compliance; either a high proportion of women in the no-epidural group received epidural or a high proportion of women in the epidural group did not receive epidural. In some cases, most of the cesarean deliveries in the no-epidural group occurred in women who actually received an epidural.[20] Such high crossover rates make findings of no association impossible to interpret.

There are also questions about the applicability of the results of these randomized trials to the general population of laboring patients, given the young age of some of the study populations,[18-20] and the high proportion of rapid deliveries.[15, 18, 19] Taken together, these facts suggest that the study populations may represent a subgroup that is not typical of women delivering at many hospitals. Overall, these randomized trials provide insufficient evidence to determine whether epidural does or does not tend to increase cesarean delivery rates.

Interpretation of observational studies is complicated by self-selection of women who receive epidurals. The most important differences identified between women who receive and do not receive epidural relate to the woman's inherent labor pattern. Women who receive epidurals tend to be admitted earlier in labor and dilate more slowly. Few studies take these and other confounding factors into account, but those that do continue to find a robust association between epidural and cesarean delivery.[23, 26, 27]

It has been suggested that women request epidural because they are having abnormal or exceptionally difficult labor and that this difficult labor is the reason why women receiving epidural experience a difference in outcomes. "Difficult labor" is challenging to measure because there is a strong subjective element to the experience of pain. Objective criteria for "difficult labor" would be likely to focus on factors that gauge the progress of labor, such as rate of cervical dilation and cervical dilation at admission. Taking these factors into account in analyses is likely to represent the best way to take differences in the "difficulty of labor" into account in observational analyses.

In addition, in deciding whether women who choose epidural have abnormal or unusually difficult labor (and therefore would be at increased risk for cesarean delivery regardless of epidural use), one must consider what proportion of the population can reasonably be categorized as having "unusually" difficult labor. It is not unreasonable to suggest that a small proportion of women have an exceptional degree of pain because of abnormal labor and request epidural as a result. However, because currently more than half of women nationwide receive epidural for pain relief during labor (and even more in large delivery services),[1] it is not reasonable to suggest that "unusual" or "abnormal" pain is the reason most women request epidural. In fact, at least 1 study indicates that many women having their first baby decide to get an epidural during pregnancy, before they could have any idea of the difficulty of their labor.[65]

Overall, existing data are insufficient to allow a determination of whether the use of epidural increases the rate of cesarean delivery. Our conclusion contrasts with that of a recent meta-analysis of RCTs[66] that concluded that there was not an association. That analysis (which did not include the 2 most recent randomized trials[15,21]) found an odds ratio (OR) of 1.5 for the association of epidural with cesarean delivery and a 95% confidence limit of .81 to 2.76. This OR indicates the best estimate we can make is that women who have an epidural are 1.5 times as likely to have a cesarean delivery. The authors' conclusion that there is "no association" was made on the basis of the lack of statistical significance (because the confidence limits include 1.0). But there are many factors that contribute to whether statistical significance is reached. For example, the choice to use a scoring system to weight articles, although use of these scores is controversial,[7, 8] may have influenced the results of the analysis. However, most important in this case is that the results of a meta-analysis can be no stronger than the studies that contribute to it. The large RCTs that contribute most of the information for the meta-analysis are not interpretable, primarily because such a high proportion of women did not get the treatment to which they were assigned. Given the problems with the individual studies, meta-analyses cannot provide an answer.

In summary, the evidence we now have does not allow us to determine whether there is an association of

epidural with cesarean delivery. Existing evidence clearly does not allow us to conclude that an association has been ruled out. The 5 large RCTs are inconclusive. Results from well-designed observational studies suggesting a possible effect cannot be ignored. It is also important to note that, if epidural does increase cesarean deliveries, the degree of increase may vary from institution to institution on the basis of differences in population characteristics and management styles.

Instrumental vaginal delivery outcomes. A higher rate of instrumental vaginal delivery (forceps and vacuum extraction) has been associated with epidural use in most studies, and the association was found to be significant in a recent meta-analysis of randomized trials.[66] There has been less concern about increases in instrumental vaginal delivery than cesarean delivery, perhaps because it is not major surgery. However, instrumental vaginal delivery may have serious consequences for the mother and infant. It is associated with a substantial increase in serious perineal lacerations in the mother[67] and with neonatal birth injuries.[68-70] In addition, vacuum delivery has been associated with the occurrence of subgaleal hemorrhage in newborns,[71, 72] as noted in a 1998 Food and Drug Administration advisory.[73]

There is tremendous variability in the baseline rate of instrumental vaginal delivery among women without epidural. Even in studies including only term, nulliparous women in spontaneous labor, the rate of instrumental vaginal delivery among women without epidural varies from 4%[23] to 60%.[38] This variation reflects differences in practice that may also influence the effect of epidural.

Randomized trials. All ten RCTs examine the association of epidural with instrumental vaginal delivery (Table II). Seven studies present data for nulliparas.[17, 20, 28-30] All have RRs >1 (range, 1.1-2.3), but not all reach statistical significance in some cases,[17, 29, 30] possibly because of small study size. The single study that presents separate results for multiparas[28] found an RR of 5.3, which was not statistically significant, but there were only 35 women in the study. Two of the 3 mixed parity studies[18,19] found an RR >1, although only one was statistically significant.[19] The only randomized study that did not find a higher rate of instrumental vaginal delivery stopped the epidurals at 8 cm to enhance pushing during the second stage.[31] Although not unequivocal, these results suggest that the use of epidural analgesia is associated with a somewhat higher risk of instrumental vaginal delivery. However, the RCTs that evaluated instrumental vaginal delivery are the same ones that examined cesarean deliveries and the same problems apply. First, 2 of the trials, Ramin et al[19] (one of the 5 larger trials) and Robinson et al,[28] did not perform intention-to-treat analyses but included only women accepting the treatment to which they were assigned. Women who accept epidural are different from those who accept opioid pain relief only. For example, in Ramin et al, nulliparous women were more likely to accept epidural, whereas multiparous women were more likely to accept only opioids. Because nulliparas have a higher rate of instrumental delivery,[74] the higher proportion of nulliparous women accepting treatment in the epidural group results in the expectation of a higher rate of instrumental delivery in that group. As expected, Ramin et al found a fairly high RR of 3.2 for the association. The failure of these studies to use intention-to-treat analysis makes them more like observational studies that require control of confounding.

For the remaining 4 large trials (Sharma et al,[18] Clark et al,[20] Loughnan et al,[21] and Howell et al[15]), the interpretability of the intention-to-treat analysis is seriously compromised by problems related to crossover. In Clark et al and Loughnan et al, more than half of the women in the no-epidural group actually received an epidural, in Sharma et al, 32% of the women in the epidural group never actually received epidural analgesia, and in Howell et al, approximately 30% of women in each randomized group did not receive the treatment to which they were assigned. When such a large proportion of women fail to receive their assigned treatment, the 2 randomized groups become much more similar, making it more difficult to detect differences in outcome.

Finally, the results of the large trials[18-20] may not be applicable to the overall population of laboring women given the young age of the subjects in some studies[18-20] and the fact that in the 3 studies that reported reasons for noncompliance,[15, 18, 19] a major reason why women did not receive their assigned treatment was that they delivered too rapidly to receive analgesia.

Observational studies. We identified 27 observational studies that evaluated the association between epidural analgesia and instrumental vaginal delivery in populations that included all women regardless of method of delivery (Table IV). Only one of them[36] failed to find a statistically significant association. For studies including only nulliparous women,[23, 24, 27, 36-41, 43, 44, 46, 47, 49-51] RRs ranged from 1.3 to 4.8. The RRs tended to be higher in studies of multiparas (range, 3.7-5.3).[38, 46, 50, 53] The 8 additional observational studies that limited the study population to women with vaginal deliveries (Table V)[75-82] all also found statistically significant associations between the use of epidural analgesia and instrumental vaginal delivery.

We identified only one observational study that controlled for confounding factors. Thorp et al[27] categorized women according to whether they were dilating slowly (< 1 cm/hour) or quickly (≥1 cm/hour) during early labor and found a strong association between epidural and instrumental vaginal delivery in both slow dilators (23% vs 4% no-epidural) and fast dilators (27% vs 9% no-epidural). This suggests that the association is not solely because of more difficult labors in women who receive epidural.

Summary: Instrumental vaginal delivery. The data demonstrating an association of epidural with instrumental vaginal

Table V. Observational studies that compare method of delivery for women with and without epidural: Studies limited to women having vaginal birth

Author (y)	*Bupivacaine conc. ± opioid (O); intermittent (I) or continuous (C)*	*#/Group epidural/ No epidural*	*All subjects low-risk**	*Inductions excluded*	*% Instrumental deliveries*		
					Epidural	*No epidural*	*RR (95% CI)*
Nulliparas							
Walton and Reynolds[75] (1984)	(I)†	821/682	N	N	52	14	3.8 (3.1,4.7)
Kaminski et al[78] (1987)	.25% (I)	125/125	Y	N	52	23	2.2 (1.6,3.2)
Paterson et al[77] (1992)	—‡	2574/8196	Y	Y	40	13	3.2 (3.0,3.5)
Robinson et al[67] (1999)	.125% + O (C)	1376/566	Y	N	21	6	3.7 (2.6,5.3)
Multiparas							
Walton and Reynolds[75] (1984)	(I)†	480/1377	N	N	26	2	14.0 (9.3,21.1)
Kaminski et al[78] (1987)	.25% (I)	30/30	N	N	43	7	6.5 (1.6,26.4)
Paterson et al[77] (1992)	—	966/13,133	N	Y	17	2	9.9 (8.2,12.0)
Mixed Parity							
Schussman et al[81] (1982)	—	320/205	N	N	50	22	2.2 (1.7,2.9)
Jouppila et al[79] (1983)	.5% (I)§	43/37	N	N	5	3	1.7 (.2,18.2)
Cox et al[80] (1987)	.125% (C) or (I†)	296/822	N	N	23	3	7.3 (4.7,11.2)
Hawkins et al[82] (1995) (I)‖	—	197/5620	N	N	41	8	4.9 (4.0,5.9)
(II)¶	—	2466/6521	N	N	33	5	6.5 (5.8,7.4)

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Unspecified concentration. ‡Information regarding epidural drugs not provided. §First-stage only. ‖Analysis I: 1979-1980 population. ¶Analysis II: 1983-1985 population.

delivery are more convincing than the data for cesarean delivery. The rate of instrumental vaginal delivery is higher in a number of RCTs despite methodologic problems related to crossover; the association also was present in all but one of the 35 observational studies we reviewed. A recent meta-analysis of RCTs also concluded that there is an association between epidural and instrumental vaginal delivery.[66] The estimated pooled odds ratio was 2.2 (95% CI, 1.3, 7.8). However, the authors also concluded that there is no association of epidural with instrumental deliveries for dystocia (OR, .7; 95% CI, .3, 1.5). These apparently contradictory results highlight some of the pitfalls of meta-analysis. The inconsistency occurs because the conclusion related to overall instrumental delivery is based on 9 randomized studies with a total of more than 2300 women, whereas the conclusion concerning dystocia is based on only 2 studies and a total of approximately 200 women. An examination of the only 2 studies used as the basis for the conclusion regarding instrumental deliveries for dystocia explains the negative finding. In the first study,[31] the epidural was allowed to wear off for the second stage of labor so that women would "retain the bearing-down reflex." In the second study,[30] a much higher overall rate of operative vaginal delivery with epidural was found (81.3% vs 54.9%), but most of them were reportedly performed for "resident training," and were therefore not included in the meta-analysis for dystocia. The report provides no further information related to indication, and therefore we do not know whether the presence of dystocia contributed to a decision to perform an operative vaginal delivery for "resident training." Because epidurals were associated with an increase in instrumental vaginal deliveries overall, unless most instrumental vaginal deliveries are performed only for resident training, there should be an increase in the rate for some other indication. The authors did not address this issue.

Overall, existing data support an association of epidural with instrumental vaginal delivery. The association is present in RCTs and in virtually all observational studies. This finding is important because of the morbidity to mother and infant that may accompany instrumental vaginal deliveries.

Spontaneous vaginal delivery outcomes. Both cesarean and instrumental vaginal deliveries have been frequently evaluated in studies of epidural. However, examining each of these interventions separately gives an incomplete picture because the use of cesarean or instrumental vaginal deliveries represents a practice choice that may vary among providers and across institutions. An alternative approach is to determine the proportion of women who delivered spontaneously, without either of these interventions. We identified 8 randomized trials and 27 observational studies that permitted such a comparison (Tables II and IV).

In 4 of the 6 randomized studies conducted in nulliparas, the proportion of women with a spontaneous vaginal delivery was substantially higher in the control group than in the epidural group,[15, 17, 29, 30] with an additional 9% to 40% of women experiencing a spontaneous vaginal delivery.[17, 29, 30] In the 2 randomized studies among nulliparas in which the rates were similar, more than half of women in the control group had received epidural,[20, 21] leading to the expectation of more similar outcomes in the 2 groups. It is more difficult to evaluate spontaneous vaginal delivery in the RCTs with mixed parity populations because all 3 studies[18, 19, 31] altered the administration of epidural in the second stage, either stopping it or decreasing it if progress was inadequate. Despite this, one

of the 3 studies[19] still found a significantly lower rate of spontaneous vaginal delivery in the epidural group.

All the observational studies we reviewed reported a lower rate of spontaneous vaginal delivery with epidural. Among nulliparous women, the difference in the proportion of women with spontaneous vaginal deliveries ranged from 5% to 65%. The differences were most marked in the 9 studies limited to nulliparas with spontaneous onset of labor, in which the proportion of women with a spontaneous vaginal delivery was at least 20% lower among women who had received epidural. In 6 of the 9 studies, <50% of women who received epidural had a spontaneous vaginal delivery.

Length of labor. We identified 25 studies that present data related to the length of labor with and without epidural. There was substantial variation in the lengths of labor reported. Differences in the definition of length of labor between studies (eg, whether the start time is based on admission to the hospital, the frequency of contractions, or a particular cervical dilatation), contributed to these differences, although other factors, such as population characteristics, may also have played a role.

Randomized trials. Eight RCTs present data related to length of labor (Table VI).[15, 17-21, 28, 31] The 2 trials,[19] reporting only overall length of labor, found longer labors in women who receive epidural. The 5 trials, reporting on the length of the first stage of labor, do not present a clear picture. Robinson et al[83] (in which the analysis was not by intention-to-treat) and Loughnan et al[21] (in which 56% of the control group received epidural) found the first stage of labor to be of similar length or somewhat shorter in women randomized to receive epidurals. The other randomized trials[15, 17, 20] all found somewhat longer lengths of labor with epidural. The largest difference in the length of the first stage was found in the trial by Thorp et al, a small study in which there was essentially no crossover between the 2 groups. Among women in the epidural group, the first stage of labor was 2.6 hours longer on average. This study also demonstrated a change in the pace of dilation between the 2 groups. Before epidural, the randomization groups were dilating at the same rate (.52 cm/hour), but after analgesia, the rate of dilation in the epidural group was slower than in the no-epidural group (1.9 cm/hour epidural, 2.7 cm/hour epidural). However, although existing studies suggest a longer length of the first stage of labor, the data available are not sufficient to provide definitive evidence.

Seven trials examined length of the second stage of labor. All found a longer second stage in the epidural group, with the difference ranging from 7 to 61 minutes. However, although these studies are randomized, methodologic issues hamper the ability of the studies to estimate the magnitude of the difference in length of labor. Philipsen and Jensen[31] stopped providing epidural medication at 8 cm, whereas 3 other trials (Sharma et al,[18] Ramin et al,[19] and Loughnan et al[21]) decreased or stopped the epidural at the onset of second-stage labor, particularly if progress was inadequate. All of these practices would tend to decrease differences between the groups in the length of second-stage labor.

In addition, all 5 large trials examining length of labor had other methodologic issues hampering interpretation. Three of the trials (Clark et al,[20] Loughnan et al,[21] and Howell et al[15]) had very high crossover rates that would make the groups more similar with regard to the length of the first and second stages of labor. The other 2 large trials (Ramin et al[19] and Sharma et al[18]) reported length of labor only for the two thirds of women who accepted the treatment to which they were assigned, probably tending to increase differences. These problems make these studies less informative.

Observational studies. The 16 observational studies that examined length of labor (Table VII) consistently report that both the first and second stage of labor are longer for women who receive epidural. Because length of labor differs by parity and whether a woman is induced, we first examined the 5 studies conducted in low-risk nulliparous women with spontaneous labor.[26, 27, 37, 41, 62] These studies provide fairly consistent results. Increases in the length of the first stage of labor range from 2.5 to 4.4 hours, and increases in the length of the second stage range from approximately 30 minutes to 45 minutes.

Two studies present separate data for length of labor in nulliparous and multiparous women. In a study of women with spontaneous and induced labor, Zimmer et al[50] found that labor was on average 2.1 hours longer for nulliparas receiving epidural, whereas it was 1.7 hours longer for multiparas. Rojansky et al[25] reported similar findings among induced women. Length of labor was 2.5 hours longer for nulliparous women but only 1.9 hours longer for multiparas who receive epidural.

Summary: Length of labor. Although existing data suggest there may be a longer first stage of labor with epidural, current evidence is insufficient to determine definitively whether that is the case. Existing data strongly support the occurrence of longer second stages of labor among women who receive epidurals. We believe that most randomized trials that have been conducted would tend to underestimate the true difference. This view is based on both the methodologic issues discussed previously and the likely nonrepresentativeness of the populations enrolled in some trials in which the women were very young[18-20] and had a high rate of very rapid delivery.[15, 18, 19] On the other hand, findings from observational studies likely overestimate the increase in length of labor, because women who choose epidural are different from those who do not and these differences were not taken into account in the analyses. The truth probably lies somewhere between the estimates from the 2 kinds of studies.

Table VI. Comparison of length of labor in randomized trials comparing epidural analgesia and opioid

Author (y)	*#/Group Epidural /Control*	*Intent-to-treat analysis*	*Epidural stopped/ decreased in 2nd stage*	*% Epidural group not receiving epidural*	*% Control group receiving epidural*	*Mean total length of labor (hr)*		
						Epidural	*Control*	*Difference*
Nulliparas								
Robinson et al[28] (1980)	28/30	N†	N	—	—	—	—	—
Thorp et al[17] (1993)	48/45	Y	N	2	0	—	—	—
Clark et al[20] (1998)	156/162	Y	N	6	52	8.4	7.5	0.9
Loughnan et al (2000) [21]	304/310	Y	Y	15	56	—	—	—
Howell et al (2001)[15]	184/185	Y	N	33	28	—	—	—
Multiparas								
Robinson et al[28] (1980)	17/18	N†	N	—	—	—	—	—
Mixed parity								
Philipsen and Jensen[31] (1989)	57/54	Y	Y	—	—	13.4‡	11.0‡	2.4
Ramin et al[19](1995)	432/437	N†	Y	35	34	7.2§	5.7§	1.5
Sharma et al[18] (1997)	243/259	N†	Y	32	1	—	—	—

*Excludes subjects not reaching full dilation. †Analysis of protocol compliant subjects. ‡Median. §Infusion halved in second stage and stopped if progress inadequate.

Table VII. Comparison of length of labor for epidural compared with no epidural in observational studies

Author (y)		*#/Group epidural/ No epidural*	*All subjects low-risk**	*Inductions excluded*	*Mean total length of labor (hr)*		
					Epidural	*No epidural*	*Difference*
Nulliparas							
Kanto et al[36] (1983)	(I)†	100/100	N	N	—	—	—
	(II)	50/50	N	N	—	—	—
Harrison et al[37] (1987)		50/20	N	N	7.7	5.2	2.5
Thorp et al[26] (1989)		447/264	Y	Y	8.6	4.7	3.9
Manyonda et al[41](1990)	(I)‡	200/200	Y	Y	—	—	—
	(II)§	200/200	Y	Y	—	—	—
Thorp et al[27] (1991)		294/206	Y	Y	—	—	—
Dickinson et al[62] (1997)		257/240	Y	Y	—	—	—
Rojansky et al[25] (1997)		38/29	N	N¶	7.4	4.9	2.5
Zimmer et al[50] (2000)		233/151	Y	N	9.5	7.4	2.1
Multiparas							
Rojansky et al[25] (1997)		74/69	N	N¶	5.5	3.6	1.9
McRae-Bergeron et al[53] (1998)		100/102	N	N	—	—	—
Zimmer et al[50] (2000)		141/322	N	N	7.1	5.4	1.7
Mixed parity							
Kanto et al[36] (1983)		102/101	N	N	—	—	—
Diro and Beydoun[54] (1985)		43/43#	N	Y	16.1	11.0	5.1
Niehaus et al[56] (1988)		110/514	N	N	—	—	—
Camann et al[85] (1991)	(I)**	20/13	Y	Y	—	—	—
	(II)††	20/13	Y	Y	—	—	—
Khan et al[57] (1993)		64/118	N	N	—	—	—
Cammu et al[16] (1994)		297/703	N	N	—	—	—
Newton et al[106] (1995)		62/124	N	N	—	—	—
Russell et al[129] (1996)		319/131	N	N	—	—	—

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Analysis I with historical control group. ‡Analysis I: 1983 study. Protocol included no boluses in 2nd-stage labor. §Analysis II: 1985 study. Delayed pushing protocol in effect. ‖Median. ¶Inductions only. #Excluded subjects with a 1st stage cesarean delivery. **Epidural with fentanyl. ‡‡Epidural without fentanyl.

Intrapartum fever. Two studies conducted in the late 1980s and the early 1990s reported an increase in maternal temperature but no evidence of infection among women who received epidural analgesia for pain relief during labor.[84, 85] However, both of these studies reported only mean increases in temperature; neither reported whether women developed fever. Several subsequent observational and randomized studies have documented a higher rate of fever among women who receive epidural (Table VIII). Fever was generally defined as a temperature of at least 38.0°C (100.4°F), except for 2 studies[86, 87] that used a threshold of 37.8°C. Two RCTs have documented an increased incidence of intrapartum fever among women who receive epidurals. Ramin et al[19] found a nearly 5-fold

Mean length of 1st stage (hr)			*Mean length of 2nd stage (min)*		
Epidural	*Control*	*Difference*	*Epidural*	*Control*	*Difference*
8.2	8.3	-0.1	54	42	12
11.3*	8.7*	2.6	115	54	61
5.2	4.6	0.6	66	59	7
8.5	9.0	0.5	78	60	18
6.5	5.8	0.7	81	62	19
6.0	6.4	-0.4	30	18	12
—	—	—	47‡	37‡	10
—	—	—	—	—	—
—	—	—	47§	38§	11

Mean length of 1st-stage (hr)			*Mean length of 2nd-stage (min)*		
Epidural	*No epidural*	*Difference*	*Epidural*	*No epidural*	*Difference*
9.5	6.5	3.0	40	25	15
6.4	5.7	0.7	41	35	6.0
—	—	—	—	—	—
—	—	—	—	—	—
10.0‖	6.3‖	3.7	65	35	30
10.2‖	6.3‖	3.9	80	37	43
8.0	5.5	2.5	84	48	36
8.4‖	4.0‖	4.4	102	72	30
—	—	—	—	—	—
—	—	—	150	96	54
—	—	—	—	—	—
—	—	—	37	15	22
—	—	—	90	48	42
8.8	5.6	3.2	37	29	8
15.1	10.3	4.8	62	45	17
—	—	—	91	39	52
—	—	—	115	60	55
—	—	—	90	60	30
6.3	5.7	0.6	18	18	0
6.9	3.3	3.6	36	31	5
—	—	—	60	30	30
7.5‖	4.2‖	3.3	67	24	43

increase in the rate of "chorioamnionitis" among women who received epidural, but the only diagnostic criterion was a fever >38°C. Philip et al[88] (analyzing data from the RCT of Sharma et al[18]) also found an increase in the rate of fever among the total group of women randomized to the epidural group, with the increase being greater among nulliparous than multiparous women. The rate of fever among women with epidural is lower in Philip et al than in Ramin et al (15% vs 23%), although the 2 studies were conducted within about one year of each other in the same institution, using the same eligibility criteria. The reason for the difference is that the analysis by Philip et al is by intention-to-treat, whereas Ramin et al included only protocol-compliant women. Because 32% of women in the epidural group in Philip et al did not actually receive an epidural, the rate of fever is likely to be an underestimate. In addition, because the rate of protocol noncompliance was higher among multiparas (45%), the underestimation of the rate of fever associated with epidural is likely to be somewhat greater in that group.

All 6 observational studies examining the occurrence of fever found higher rates of fever with epidural.[86, 89-92] RRs for nulliparous women vary from 5.0 to 70.8. However, much of the variation in the RR is caused by variation of the rate of fever in the no-epidural group. In the RCTs of Ramin et al[19] and Philip et al[88] the rate of fever among women without epidural is 5%, whereas in the study of Gonen et al[87] (the study with the highest RR), the rate of fever in women not receiving epidural is only 0.2%. The rate differences in these studies (the additional proportion of women who become febrile in the epidural group) are similar, ranging from 11% to 19% among nulliparous women.

In addition, the literature suggests that epidural is responsible for a high proportion of fever during term labor. Both Lieberman et al[92] and Gonen et al[87] found that more than 95% of fever in their term populations occurred in women who had received epidural. Epidural-related fever is generally believed to result from thermoregulatory alterations rather than infection.[84, 90, 93, 94] Although some have hypothesized an infectious etiology[22, 95] because of the longer labors and longer time with ruptured membranes that occur with epidurals, if that were the case a high proportion of women with long labor but no epidural should also have fevers. The data of Lieberman et al[92] indicate that is not the case (Fig 2) and that the rate of fever among women without epidural remains low regardless of length of labor. The failure of temperature to increase in women who do not receive epidural is also supported by Fusi et al[84] and Camann et al[85]

Maternal fever could contribute to a higher rate of cesarean and instrumental vaginal deliveries with epidural. Lieberman et al[96] examined the association of temperature elevation with cesarean and instrumental vaginal deliveries in a population of 1233 low-risk, nulliparous women in term, spontaneous labor. Women with temperatures >99.5°F were 3 times as likely to have a cesarean delivery (25% vs 7%) and 3 times as likely to have an instrumental vaginal delivery (25% vs 9%). Ninety percent of women with an elevated temperature had received epidural. The association remained after controlling for confounding factors in a multivariate analysis.

Table VIII. Results of studies examining epidural and fever during labor

Author (y)	#/Group epidural/ No epidural	Population	All subjects low-risk*	Inductions excluded	% fever (temperature >38°C or 100.4°F) Epidural	No Epidural	RR (95% CI)	RD (%)
Randomized trials								
Ramin et al[19] (1995)	432/437†	Mixed parity	Y	Y	23	5	4.7 (3.0,7.4)	17.9
Philip et al[88] (1999)								
(I)	358/357	Mixed parity	Y	Y	15	4	3.9 (2.2,6.8)	11
(II)	197/189	Nulliparas	Y	Y	24	5	5.0 (2.5,9.9)	19.1
(III)	161/168	Multiparas	Y	Y	4	3	1.5 (0.5,4.5)	1.4
Observational studies								
Macauley et al[90] (1992)	32/24	Mixed parity	N	N	9	0	—	9.1
Vinson et al[89] (1993)	41/36	Mixed parity	N	N	15	0	—	14.6
Herbst et al[91] (1995)	683/2426	Mixed parity	N	N	6	1	5.6 (3.5,8.9)	5.3
Lieberman et al[92] (1997)	1047/610	Nulliparas	Y	N	15	1	14.8 (6.5,33.2)	13.5
Mayer et al[86] (1997)	194/96	Nulliparas; vaginal delivery only	Y	N	20	2	9.8 (2.4,39.7)	18.0
Gonen et al[87] (2000)	406/598	Mixed parity	N	N	12	0.2	70.8 (9.8, 510)	11.6

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar.
†Protocol compliant subjects only.

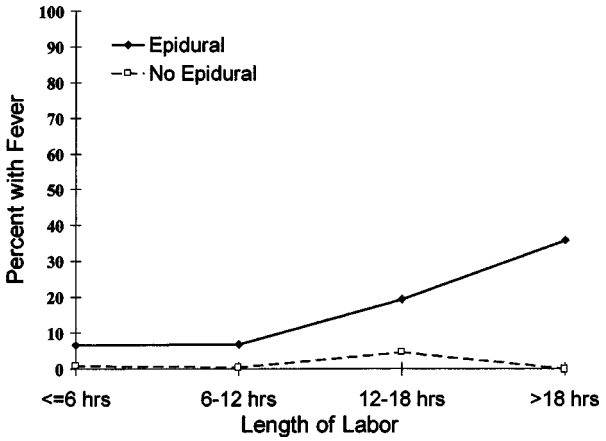

Fig 2. Percent of nulliparous women with fever >100.4°F according to length of labor and epidural use. Reproduced by permission of Pediatrics 1997;99:415-9.

Even if not of infectious origin, epidural-related fever has consequences for mother and infant. Because it is not possible during labor to distinguish with confidence between infectious and noninfectious fever, women who receive epidural are more frequently treated with intrapartum antibiotics. Mayer et al[86] found that term nulliparous women who receive epidural were more than 3 times as likely to receive intrapartum antibiotics (20% versus 6%). Neonatal consequences of maternal intrapartum fever are discussed in Section III of this paper.

Summary: Intrapartum fever. An increase in fever with epidural has been documented in both randomized trials and observational studies. The association is consistent, suggesting a causal link, although the exact mechanism has not been established. The evidence suggests that among nulliparous women, an additional 10% to 15% of women (above the baseline rate) will become febrile. This is likely to contribute to the higher rate of intrapartum antibiotic use among women who receive epidural and may contribute to a higher rate of cesarean delivery and operative vaginal delivery among women who receive epidural.

Fetal malposition. Fetal malposition, particularly occiput posterior position, has been associated with higher rates of cesarean[97] and instrumental vaginal deliveries.[98] If epidural is associated with a higher rate of fetal malposition, it could represent a mechanism by which epidural increases the rate of cesarean or instrumental vaginal deliveries. We identified 7 studies that examined this issue (Table IX).

Randomized trials. Three RCTs present data on the association of epidural with fetal malposition (occiput posterior or occiput transverse position).[17,30] Thorp et al[17] found a 4-fold increase in the rate of malposition in the epidural group (19% vs 4%). The 2 other randomized trials found smaller differences. Bofill et al[30] reported a 22% rate of fetal malposition in the epidural group compared with 18% in the no-epidural group; Howell et al[15] found a 16% rate of malposition with epidural and a 14% rate without epidural. However, both of the latter studies had substantial crossover. In Bofill et al, 24% of the women in the control group received epidural and in Howell et al, about 30% of women in each group did not receive the treatment to which they were assigned. The high proportion of women in the control group who actually received epidurals in these 2 studies could have contributed to the relatively high rate of fetal malposition in the no-epidural groups.

Observational studies. Two observational studies examined the rate of malposition in overall populations of laboring women. In a study of 500 nulliparous women, Thorp et al[27] found approximately twice the rate of fetal malposition among women who had received epidural (17% vs 9%). Kanto et al[36] present data for 3 separate populations. In 2 of the populations (1 nulliparous and 1 mixed parity), women

Table IX. Results of studies examining the association between epidural and fetal malposition at delivery

Author (y)	*#/Group epidural/ No epidural*	*Population*	*All subjects low-risk**	*Inductions excluded*	*% Control group receiving epidural/ % epidural group not receiving epidural*	*% malposition (OP or OT presentation)*		
						Epidural	*No Epidural*	*RR (95% CI)*
Randomized Trials								
Thorp et al[17] (1993)	48/45	Nulliparous	Y	Y	0/2	19	4	4.2 (1.0, 18.5)
Bofill et al[30] (1997)	49/41	Nulliparous	Y	Y	24/4	22	18	1.3 (.6, 2.8)
Howell et al[15] (2001)	184/185	Nulliparous	Y	N	28/33	16	14	1.1 (.7, 1.9)
Observational Studies								
Thorp et al[27] (1991)	294/206	Nulliparous	Y	Y	—	17	9	1.9 (1.1, 3.1)
Kanto et al[36] (1983) (I)	50/50	Nulliparous	N	N	—	0	0	—
(II)†	100/100	Nulliparous	N	N	—	6	3	2.0 (.5, 7.8)
(III)	102/101	Mixed parity	N	N	—	5	3	1.7 (.4, 6.7)
Observational Studies–Cesarean deliveries excluded								
Schussman et al[81] (1982)	320/205	Mixed parity	N	N	—	11	14	0.8 (.5, 1.3)
Kaminski et al[78] (1987)	155/155	Mixed parity	N	N	—	27	8	3.5 (1.9, 6.4)
Khan et al[57] (1993)	56/100	Mixed parity	N	N	—	25	7	3.6 (1.5, 8.3)

**Low-risk*, term, singleton, cephalic. †Analysis II: historical controls.

receiving epidural had higher rates of malposition, similar to those of Thorp et al (RR, 2.0 and 1.7), but the differences do not reach statistical significance. In a third, smaller population of nulliparas, no cases of fetal malposition occurred either with or without epidural.

Malposition was also examined in 3 observational studies that included only women with vaginal deliveries.[57, 78, 81] Two reported an increase in fetal malposition among women who receive epidural.[57, 78] However, these estimates are difficult to interpret because fetal malposition may sometimes lead to cesarean delivery, and the percent of women excluded for this reason could differ in the epidural and no epidural groups.

Summary: Fetal malposition. Fetal malposition represents a potential mechanism by which epidural could increase cesarean and operative vaginal deliveries. One small RCT found a significant association. The other 2 RCTs examining this issue are difficult to interpret because of high rates of crossover. Observational studies tend to find higher rates of malposition among women who receive epidurals but are difficult to interpret because they cannot distinguish whether epidural results in fetal malposition or women with fetal malposition are more likely to request an epidural. Because fetal malposition has been associated with an increase in maternal and neonatal morbidity,[99] it is important that further study clarify these associations.

Perineal laceration. Perineal trauma at birth involving the anal sphincter (3rd- and 4th-degree perineal lacerations) may have long-term consequences for the woman giving birth. Such lacerations have been associated with a higher likelihood of incontinence when compared with birth with an intact perineum,[100] and studies have suggested that the problems may persist for decades.[101]

Third- and 4th-degree perineal lacerations are more likely when instrumental vaginal delivery is performed.[67] Because existing data support an increase in instrumental vaginal delivery when epidural is used, epidural may also influence the rate of serious perineal lacerations. Few articles have evaluated this association (Table X). Overall, we identified 7 studies examining this issue, including 1 case control study,[102] 4 cohort studies[24, 55, 76, 103] that included all women with vaginal deliveries, and 1 cohort study that included all laboring women. The seventh study, Combs et al,[104] included only women with instrumental vaginal deliveries[104] and must be considered separately.

Five of the 6 studies not limited to instrumental vaginal deliveries found an association of epidural with perineal laceration with the RRs, suggesting approximately a 2-fold increase.[55, 76, 103] Although the difference in the study of Bright et al[55] is not statistically significant, the numbers are smaller than in the other studies. Robinson et al,[76] who studied 1942 term nulliparous women, found that the association remained significant in a logistic regression analysis controlling for potential confounding factors (OR, 1.4; 95% CI, 1.0, 2.0).

Robinson et al[76] also demonstrate the pathway for the association. They classified women into 4 categories by method of delivery (spontaneous or instrumental) and the use of episiotomy (yes/no) and then, for each category, compared the rate of severe perineal lacerations for women receiving and not receiving epidural. Both instrumental vaginal delivery and episiotomy were much more frequent in women receiving epidural but once these 2 practices were taken into account, epidural was not associated with any further increase in 3rd- and 4th-degree perineal lacerations. This also explains the lack of association in Combs et al.[104] Because their study was limited to women with instrumental vaginal deliveries, a difference in perineal lacerations would not be expected with and without epidural. Similarly, once instrumental vaginal delivery is controlled in regression analyses,[102] one would

Table X. Results of studies examining the association of epidural with perineal lacerations*

Author (y)	#/Group epidural/ No epidural	Population	% 3rd- or 4th-degree perineal lacerations		
			Epidural	No epidural	RR (95% CI)
Legino et al[103] (1986)	436/4200	Mixed parity	37	14	2.7 (2.4,3.1)
Combs et al[104] (1990)	1876/925	Mixed parity; limited to instrumental vaginal delivery	28	34	.8 (.7,.9)
Bright[55] (1993)	100/100	Mixed parity	7	3	2.0 (.5,7.7)
Lyon et al[24] (1997)	247/174	Nulliparous	12	13	1.0 (.6,1.7)
Robinson et al[76] (1999)	1376/566	Nulliparous	16	10	1.7 (1.3,2.2)
Samuelsson et al[200] (2000)	772/2111	Mixed parity	5	3	2.2 (1.5,3.2)

*Study populations include only vaginal deliveries except for Samuelsson, which includes all women intending a vaginal delivery at admission; data for Ural et al[102] not shown because it is a case control study.

not be expected to show an association of epidural with perineal laceration.

Summary. The evidence suggests that epidural use is associated with an increase in 3rd- and 4th-degree perineal lacerations. The association is present in most studies and there is a logical mechanism to explain it. Although there is not sufficient information to evaluate why Lyon et al[24] did not find an association, a number of factors, especially instrumental delivery and episiotomy, may modulate the association.

Fetal outcomes. The effect of epidural analgesia on the fetus is more difficult to evaluate than its effects on the mother. Research has evaluated 2 factors related to fetal status, fetal heart rate (FHR) abnormalities and the presence of meconium-stained amniotic fluid. Immediately after birth, it is possible to examine arterial and venous cord pH and Apgar scores. We will also comment on the use of naloxone hydrochloride (HCl).

FHR changes. Few studies have examined the association of epidural with FHR patterns. Rojansky et al[25] found a similar rate of "fetal heart rate changes" among induced women with and without epidural (16% epidural, 13% no epidural) but did not define what FHR changes were included. In a study of 200 women, Spencer et al[105] found a significantly higher proportion of fetuses with baseline heart rates >160 bpm during the second stage of labor among women with epidural (16% epidural, 3% no-epidural; RR, 5.2; 95% CI, 1.8, 15.6). Tachycardia was also more common during the last hour of the first stage of labor (7% epidural, 2% no-epidural), although this difference did not reach statistical significance rate (RR, 2.9; 95% CI, .7, 11.8). They also reported a higher proportion of fetuses with late or variable decelerations among women with epidural during both the last hour of the first stage (47% vs 13%; RR, 3.7; 95% CI, 2.2, 6.2) and the second stage of labor (66% vs 41%; RR, 1.6; 95% CI, 1.2, 2.1). Similarly, Mayer et al[86] examined a group of 287 nulliparous women with vaginal deliveries and found a higher rate of fetal tachycardia among women with epidural (6% vs 0%, $P = .02$). The rate of fetal tachycardia was not influenced by the use of narcotic pain relief.

Meconium-stained amniotic fluid. None of the 5 studies we identified that reported on the presence of meconium stained amniotic fluid found any difference in the prevalence of this finding in women with and without epidural (Table XI).[15, 18, 20, 25, 26]

Umbilical cord pH. Six RCTs[17-20, 29, 31] and 4 observational studies[24, 26, 27, 106] compared epidural and no-epidural groups for mean umbilical cord pH or the proportion of cases with a pH that was below a cutoff level, generally an umbilical arterial pH <7.15 or umbilical venous pH <7.2. No study found a significant difference between women receiving and not receiving epidural.

Apgar scores. More than 34 studies were identified in which the Apgar scores of infants whose mothers received epidural were compared with those of infants whose mothers did not receive epidural.[15, 17-20, 22, 24-27, 30, 31, 36, 38, 54, 55, 57, 63, 78-81, 105-119] Only one of these studies reports a significant difference, with a higher proportion of infants whose mothers received epidural having a 5-minute Apgar <7.[116] However, the actual difference in the proportion of infants is quite small (1.6% epidural vs 1.1% no-epidural) and statistical significance was achieved only because of the very large sample size.

Use of Naloxone HCl. One conclusion of the meta-analysis by Halpern et al[66] was that there was an increased need for naloxone HCl among infants receiving opioid. Although infants of women who receive opioids do sometimes require naloxone HCl to reverse its effects, the estimate provided by the meta-analysis is too high. Their conclusion is essentially based entirely on the study of Sharma et al[18] (because in Bofill et al,[30] the only other study noted to report naloxone HCl use, only one infant required naloxone HCl). In Sharma et al, the alternative to epidural was patient-controlled intravenous analgesia. Their use of narcotic differs from the other studies because the permissible doses of narcotic were higher and patients were permitted to continue administration until delivery. High doses of narcotic administered until delivery will predictably result in rates of naloxone HCl use that are higher than when narcotics are stopped near delivery.

Table XI. Results of studies examining the association of epidural and meconium during labor

Author (y)	*#/Group epidural/ no epidural*	*Population*	*All subjects low-risk**	*Inductions excluded*	*% Meconium*		
					Epidural	*No epidural*	*RR (95% CI)*
Randomized							
Sharma et al[18] (1997)	358/357	Mixed parity	N	Y	18	19	1.0 (.7, 1.3)
Clark et al[20] (1998)	156/162	Nulliparous	Y	Y	20	18	1.1 (.7, 1.8)
Howell et al[15] (2001)	176/181	Nulliparous	Y	N	4	3	1.4 (.5, 4.5)
Observational							
Thorp et al[26] (1989)	447/264	Nulliparous	Y	Y	23	20	1.2 (.9, 1.5)
Rojansky et al[25] (1997)	112/98	Mixed parity	N	N†	9	7	1.3 (.5, 3.2)

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Inductions only.

Table XII. Comparison of length of labor and instrumental vaginal delivery in randomized studies examining discontinuation of epidural late in labor

Author (y)	*#/Group Continue†/ wear-off‡*	*Protocol for discontinued group**	*% Excellent or good pain relief in 2nd stage*		*% Mean length 2nd stage (minutes)*			*% Instrumental delivery*		
			Continue	*Wear-off*	*Continue*	*Wear-off*	*Difference*	*Continue*	*Wear-off*	*RR (95% CI)*
Phillips and Thomas[122] (1983)	28/28	.25% bupivacaine; no boluses when fetal head below ischial spines	§	§	84	81	3	25	43	.6 (.3, 1.3)
Chestnut et al[123] (1987)	26/27	.75% lidocaine; saline solution infusion at 8 cm	46	41	73	76	-3	31	33	.9 (.4, 2.0)
Chestnut et al[108] (1987)	46/46	.125% bupivacaine; saline solution infusion at 8 cm	82	41	124‖	94‖	30	46	24	1.9 (1.0, 3.5)
Johnsrud et al[120] (1988)	90/90	.25% bupivacaine; no epidural infusion in 2nd stage	76	79	38¶	37¶	1	26	26	1.0 (.6, 1.7)
Chestnut et al[109] (1990)	29/34	.0625% bupivacaine + .0002% fentanyl; saline solution infusion at full dilation	70#	50#	53‖¶	63‖¶	–10	21	15	1.4 (.5, 4.1)
Luxman et al[121] (1996)	35/35	.25% bupivacaine; no boluses after 8 cm	—	—	43	38	5	14	17	.8 (.3, 2.5)

*Doses are those for drip or for maintenance boluses. †Group in which the epidural was allowed to continue. ‡Group in which the epidural medication was discontinued. §Measured as average pain score on 200 mm visual analog score; average pain score for continue = 40, wear-off = 150. ‖Excludes women with cesarean deliveries. ¶Median. #Numbers are estimated from figure because no numbers are provided.

Summary: Fetal outcome. Measures of fetal outcome taken immediately after birth do not indicate a difference in well-being associated with epidural use. No differences were found between infants of women receiving and not receiving epidural for either cord pH values or Apgar scores. The few studies examining the presence of meconium-stained amniotic fluid have also not noted any difference. There is some evidence of an increase in FHR abnormalities among women who receive epidural. The higher proportion of women with fetal tachycardia is likely to reflect the increase in maternal temperature that accompanies epidural use because FHR is highly correlated with maternal temperature.[84] A single study noted an increase in late or variable decelerations. This should be followed up to determine if this finding is present in other populations.

Epidural Techniques And Labor Outcomes

In this section, we consider whether specified alterations in the use of epidural are associated with differences in outcome. We will specifically consider the effect or lack of effect of (1) the discontinuation of epidural late in labor, (2) the timing of administration, (3) the use of "light" versus "standard" epidural, (4) intermittent versus continuous infusion, and (5) the use of a combined spinal-epidural technique.

Discontinuation of epidural late in labor. One potential mechanism by which epidural could exert an effect on method of delivery is by decreasing the woman's ability to push during second-stage labor. Several studies have examined whether discontinuing epidural late in the first stage (at or after 8-cm dilation) or at full dilation increases the rate of spontaneous vaginal delivery in women who receive epidurals. Six RCTs have examined the effects of discontinuing epidural late in labor (Table XII). Three of them excluded women with cesarean deliveries and examined only instrumental vaginal deliveries,[120-122] whereas the other 3 also present data on the rate of cesarean deliveries.[108, 109, 123]

The first RCT examining this issue, conducted by Philips et al,[88] excluded women delivered by cesarean. All

56 women enrolled received an epidural early in labor with an intermittent bolus technique. They were randomized to have their epidural continued or to stop receiving additional anesthetic boluses when the fetal head descended below the ischial spines. Women who continued to receive epidural had lower rates of forceps delivery (25% vs 43%) and fetal malposition (occiput posterior or occiput transverse) at delivery (7% vs 21%), as well as a first stage of labor that was slightly shorter (10.2 vs 10.5 hours). None of the differences were statistically significant. However, there are some problematic aspects to this study. The method of randomization, shuffled sheets that were used in order, would seem to be subject to easy manipulation, and in fact, examination of the 2 randomized groups reveals several important differences. Women randomized to have their epidural discontinued were twice as likely to have an induction, were less likely to have maternal choice as the indication for epidural, were younger, and had larger babies. None of these differences were taken into account in the analysis. Overall, this trial provides little information of value.

The second trial was 1 of 3 performed by Chestnut et al,[123] who enrolled 53 term, nulliparous women with singleton vertex fetuses. All women received epidural during early labor and at 8 cm, were randomized to receive either continued infusion of .75% lidocaine or saline solution. The study was conducted in a double-blind manner. The authors found no difference in the rate of instrumental vaginal delivery (31% lidocaine, 33% saline solution), second-stage cesarean delivery (0% lidocaine, 4% saline solution), fetal malposition (8% lidocaine, 7% saline solution), or mean length of the second stage of labor (73 min lidocaine, 76 min saline solution). There was no suggestion of any difference in fetal outcome as measured by both umbilical arterial or venous pH and the presence of meconium-stained amniotic fluid. However, as noted by the authors, interpretation of this study is complicated by the presence of carryover analgesia. The authors found essentially no difference between the groups in the percentage of women reporting excellent or good pain relief (46% with continued anesthesia, 41% with saline solution), suggesting that the groups might have been too similar for any difference to be detected.

Chestnut et al[108] performed a second study of similar design (n = 92), this time with women randomized at 8 cm to either saline solution or .125% bupivacaine (as opposed to lidocaine used in the earlier study). In addition, subjects in each group who lacked perineal anesthesia at complete dilation were given a bolus of study solution (.5% bupivacaine or saline solution according to randomization group). In this study, there was a difference in the proportion of women reporting excellent or good pain relief during the second stage (82% bupivacaine, 41% saline solution). Although the authors found no difference in the rate of cesarean delivery after 8 cm (13% in each group), there was a significantly higher rate of instrumental vaginal delivery in the bupivacaine group (46% vs 24%), and the second stage of labor was prolonged by an average of 30 minutes (124 min vs 94 min). There was no difference in the occurrence of fetal malposition (15% bupivacaine, 13% saline solution) and no suggestion of any difference in fetal outcome as measured by both umbilical arterial or venous cord pH and the presence of meconium-stained amniotic fluid.

In a third study, Chestnut et al[109] randomized 63 women at full dilation to receive either "light" epidural (.0625% bupivacaine + .0002% fentanyl) or saline solution during the second stage of labor. There was a small, but statistically significant difference in the proportion of women reporting excellent or good pain relief during the second stage of labor (approximately 70% bupivacaine-fentanyl, 50% saline solution). However, the improved analgesia was present only among women who had a second stage longer than 1 hour, suggesting carryover analgesia during the early second stage. There was no significant difference between the groups in the rate of second-stage cesarean delivery (3% bupivacaine-fentanyl, 0% saline solution), instrumental vaginal delivery (21% bupivacaine-fentanyl, 15% saline solution) or fetal malposition (7% bupivacaine-fentanyl, 9% saline solution). The data related to length of labor are a bit more difficult to understand. Although for women in the bupivacaine-fentanyl group the median length of the second stage was 10 minutes shorter (53 min vs 63 min), the proportion of women with a prolonged second stage (≥180 min) was substantially higher in that group (18% bupivacaine-fentanyl, 3% saline solution; $P = .08$). The authors conclude, and we agree, that these data suggest that there may have been some prolongation of the second stage. There was no difference in fetal outcomes.

Two studies of discontinuation conducted by other groups provide limited information. Johnsrund et al[120] randomized 90 term nulliparous women receiving epidural (continuous infusion of .25% bupivacaine) during the first stage of labor to either continue or have their epidural infusion stopped during the second stage. Women with cesarean delivery were excluded. The authors found no significant differences in the rate of instrumental vaginal delivery, the rate of fetal malposition or the average length of second-stage labor. However, because a similar proportion of women in each group also reported excellent or good pain relief during the second stage of labor, the finding of no difference between the groups is difficult to interpret.

Luxman et al[121] randomized 70 term nulliparous women in spontaneous labor to receive their last epidural bolus by 8 cm or to continue receiving epidural boluses throughout the second stage. However, the author notes that after randomization, women had their pain assessed by visual analog scale (range, 0-10). Women remained in

the "continue epidural" group only if their pain score was <3, whereas women were retained in the "stop epidural" group only if their pain score was >3. This unusual method of allocation created an inequality between the groups. Thus, although the authors reported no difference in the rate of instrumental vaginal delivery or the length of the second stage, it is impossible to know how to interpret the results.

Summary: Discontinuation of epidural late in labor. The primary aim of discontinuing epidural late in labor would be to increase the rate of spontaneous vaginal delivery by enhancing the woman's ability to push during second-stage labor. The best information on whether this works is provided by the 3 well-conducted studies by Chestnut et al,[108, 109, 123] which, unfortunately, yielded somewhat differing results. One of the 3 studies[108] found a difference in outcome, specifically, an increased rate of operative vaginal delivery and longer second stages among women continuing to receive anesthetic. The other 2 studies found no objective differences in outcome. There are 2 potential explanations for the differences between studies. Each of the 3 studies used a different drug regimen in the treatment group (.75% lidocaine, .125% bupivacaine, .0625 bupivacaine with fentanyl) and this difference in treatment could be the explanation for the difference in the findings of the studies because earlier studies had demonstrated an increase in length of the second stage with .125% bupivacaine compared with .75% lidocaine.[108] Alternatively, it is possible that the presence of carryover analgesia in the saline solution placebo group explains the negative finding in 2 of the studies. Because there was little difference in the reported quality of analgesia for women in the treatment and placebo arms of those 2 studies, it is possible that the levels of local anesthetics were also similar in the 2 groups, in which case similar outcomes would be expected. However, although carryover analgesia hinders interpretation of the results, these studies provide information that is clinically relevant because it would likely be impractical to discontinue analgesia earlier than 8-cm dilation. In addition, it is important to note that no study found a difference in fetal outcome between the 2 groups.

Timing of epidural administration. It has been suggested that delaying administration of epidural might decrease any potential effects on labor and method of delivery.

Randomized trials. We identified 2 randomized studies comparing early and late epidural, both conducted by Chestnut et al.[124, 125] Both studies were limited to nulliparous women who requested epidural at 3- to 5-cm cervical dilation. One study included only women who were already receiving oxytocin for either induction or augmentation at the time of enrollment, whereas the other study included only women in spontaneous labor who were not receiving oxytocin at enrollment. Women were randomized to either the "early" group, which received epidural analgesia immediately, or the "late" group, which received intravenous narcotic at enrollment with the intention that they would not receive epidural medication until they were dilated at least 5 cm. Neither study found a difference in the rates of cesarean delivery, instrumental vaginal delivery, fetal malposition, or the length of second-stage labor. There was also no difference in fetal outcome as measured by both umbilical arterial or venous pH and the presence of meconium-stained amniotic fluid.

Although these studies were technically well-conducted, there are major problems with interpretation of the data. First, many women in the late group received epidural medication before 5 cm dilation. This was permitted by the protocols of both studies, which included a provision that women in the late group could request epidural as soon as 2 hours after enrollment. As a consequence, there is only a small difference in timing between the early and late epidural groups. In the study among women receiving oxytocin, the median cm at epidural was 3.5 cm for the early group and 5.0 cm for the late group. In the spontaneous labor study, the difference in timing was even smaller; the median dilation at epidural was 4 cm in the early group and 5 cm in the late group. Given a small difference of only one cm in dilation, particularly of a measurement that is inexact and was made by an examiner aware of the study group, one would not expect there to be a difference in the method of delivery. Lack of difference in outcomes based on this small degree of difference is an inadequate basis for concluding that timing does not matter.

Observational studies. We identified 10 observational studies that evaluate early versus late epidural placement (Table XIII). Two measures were used to examine the role of the timing of epidural, centimeter dilation (<4 or 5 cm), or station of the fetal head (<0 station).

Findings relevant to cesarean delivery. All 9 studies examining the association of epidural timing with cesarean delivery among nulliparous women[17, 23, 27, 48, 49, 52, 83, 126, 127] reported a higher rate of cesarean delivery with earlier epidural. Most studies reported RRs between 1.6 and 2.2, although not all of the differences were statistically significant; 2 studies reported higher RRs of 3.0 and 4.6.[52, 83] Traynor et al[52] examined the association of timing and cesarean delivery in a continuous manner and found a steady decrease in cesarean delivery rate with later epidural placement as measured either by centimeters dilated or the station of the fetal head.

As with all observational studies, the potential for confounding factors must be considered. Thorp et al,[27] in a study that included approximately 300 women who received epidurals, examined the role of timing while taking labor characteristics into account by dividing women into 2 groups according to whether they were dilating at

Table XIII. Results of studies examining the effect of timing of epidural administration in observational studies

Author (y)		#/Group Early/ Late	Definition of Early	All subjects low-risk*	Inductions excluded	% Instrumental deliveries			% Cesarean deliveries		
						Early	Late	RR (95% CI)	Early	Late	RR (95% CI)
Nulliparas											
Thorp et al[27] (1991)		215/79	≤5 cm	Y	Y	28	14	2.0 (1.1, 3.7)	20	13	1.6 (.9, 3.1)
Thorp et al[17] (1993)		34/13	<5 cm	Y	Y	—	—	—	32	0	—
Lieberman et al[23]	(I)	286/611	<5 cm	Y	Y	—	—	—	22	14	1.7 (1.2, 2.2)
(1996)	(II)	396/501	<0 station	Y	Y	—	—	—	23	11	2.2 (1.6, 3.0)
Robinson et al[83] (1996)		82/83	<0 station	Y	N	27	24	1.1 (.7, 1.9)	22	5	4.6 (1.6, 12.9)
Rogers et al[126] (1999)		179/76	≤4 cm	Y	Y	22	14	1.5 (.8, 2.8)	15	8	1.8 (.8, 4.3)
Seyb et al[48] (1999)		427/859	<4 cm	Y	N	—	—	—	19	9	2.1 (1.7, 3.4)
Sheiner et al[127] (1999)		29/37	<0 station	Y	N	10	8	1.3 (.3, 5.9)	10	5	1.9 (.3, 10.7)
Walker et al[49] (1999)		31/34	<5 cm	Y	Y	16	35	0.5 (.2, 1.2)	45	24	1.9 (.9, 3.9)
Traynor et al[52]	(I)	449/827	<5 cm	Y	N	—	—	—	18	9	1.9 (1.4, 2.5)
(2000)	(II)	716/560	<0 station	Y	N	—	—	—	17	6	3.0 (2.1, 4.4)
Multiparas											
Robinson et al[83] (1996)		88/67	<0 station	N	N	10	15	0.7 (.3, 1.6)	14	3	4.7 (1.1, 20.2)
Sheiner et al[127] (1999)		37/28	<0 station	Y	N	5	4	1.5 (.1, 15.9)	8	11	0.8 (.2, 3.5)
Mixed parity											
Holt et al[201]	(I)	132/143	<5 cm	Y	Y	—	—	—	26	17	1.5 (.9, 2.3)
(1999)	(II)	129/146	<0 station	Y	Y	—	—	—	33	11	3.0 (1.8, 5.1)

*_Low-risk_, term, singleton, cephalic. For multiparous women, no history previous uterine scar.

<1 cm/hour or ≥1 cm/hour early in labor. Within each group, the authors compared women who received early epidurals (≤5 cm) or later epidurals (>5 cm). For slow dilators, early administration of epidural was associated with a higher rate of cesarean delivery than late epidural (24% vs 7%; $P = .01$), but for fast dilators, the timing of epidural administration made no difference in the rate of cesarean delivery (14% early epidural, 11% late epidural; $P = .7$). These data suggest that for women with an adequate rate of dilation in early labor, the timing of epidural may not influence outcome. It is important to note however, that even for those women who were dilating more quickly, the rate of cesarean delivery was higher than for women who did not receive epidural.

Instrumental vaginal delivery. Five observational studies consider the effect of epidural timing on instrumental vaginal delivery.[27, 49, 83, 126, 127] Most studies found no significant difference in the rate of instrumental delivery for women receiving early compared with late epidural analgesia for either nulliparous or multiparous women. Only the study by Thorp et al[27] found a significantly higher rate among women who received early epidural (28%) versus late epidural (14%). The increase was present both for women dilating slowly and for those dilating rapidly in early labor, although these subgroup differences were not statistically significant, possibly because of smaller sample size. Although none of the other 4 studies examining nulliparous women found significant differences in the instrumental vaginal rate based on the timing of epidural placement, they tended to have RRs >1. Available data are insufficient to determine whether timing of epidural predicts the rate of instrumental vaginal delivery, but suggest that if there is an association, it is likely to be modest.

Progress of labor. No consistent pattern emerges from the results of the few studies that have examined the effect of the timing of epidural placement on length of labor. Thorp et al[27] examined this association separately for women dilating <1 cm/hour and those dilating ≥1 cm/hour in early labor. They found a somewhat longer length of labor for slow dilators who received early epidural (9.2 hr early vs 7.9 hr late), but no difference for women who were dilating more rapidly in early labor (5.7 hr early vs 5.8 hr late). Robinson et al[83] found no significant difference in the length of the second stage for women with early epidural compared with late epidural (76 min early vs 68 min late). Sheiner et al[127] reported somewhat shorter labors among women who received early epidural (4.3 hr vs 5.8 hr), but the difference was not statistically significant.

The inconsistent findings of these studies may be caused by confounding factors. One of the important differences between women who choose to have epidurals compared with women who do not is the early pattern of their labor. The study of Thorp et al[27] suggests that this may be an important factor modifying the effect of the timing of epidural placement on the progress of labor. Further studies would be needed to determine whether this finding is consistent across populations.

Fetal malposition. Only 2 studies reported the rate of fetal malposition for early compared with late epidurals. Robinson et al[83] found that early epidural was associated with a higher rate of fetal malposition among both nulliparas (32% vs 12% for later epidurals) and multiparas (16% vs 3% for later epidurals). In contrast, in a population that included both nulliparous and multiparous women, Sheiner et al[127] found no difference in the occurrence of fetal malposition (8% early vs 11% late).

Summary: Timing of epidural administration. For this question, the RCTs that have been conducted provide little information because there was so little difference in the time of placement for the "early" epidural and "late" epidural groups. Observational studies suggest that early epidural may be associated with a higher cesarean delivery rate. Data on instrumental vaginal delivery do not present a clear pattern but suggest that if any association is present, it is probably modest. Findings on length of labor are inconsistent but suggest that the effect of timing may vary depending on a woman's inherent labor pattern. There are insufficient data to make any determination about an effect of the timing of epidural administration on fetal malposition.

"Light" versus "standard" epidural. "Light" epidural analgesia refers to epidurals using a lower concentration of local anesthetic (most commonly .0625% bupivacaine) with the addition of opioid. It was hypothesized that this combination would provide adequate analgesia with a decrease in motor block and might avoid the prolonged second stage and higher rate of instrumental vaginal delivery that had been reported in earlier studies employing .125% bupivacaine.

Four RCTs have been conducted comparing outcomes of "standard" and "light" epidural analgesia (Table XIV).[44, 59, 107, 128, 129] For all of these studies, women in the "light" epidural group received .0625% bupivacaine, although the type and dose of opioid varied. None of the studies found a significant difference in the proportion of women with instrumental vaginal delivery or cesarean delivery. There were also no significant differences noted in the length of labor. However, the first stage of labor was consistently longer, with "light" epidural suggesting the possibility there might be a small increase in length. None of the studies found a difference in fetal outcome as measured by the presence of meconium-stained amniotic fluid,[128] differences in umbilical arterial or venous pH,[107, 128, 129] or the presence of FHR abnormalities.[129]

Intermittent versus continuous infusion. Continuous infusion epidural analgesia was introduced to try and overcome some disadvantages of intermittent administration of boluses.[130] These disadvantages include a period of increasing pain for the patient before each bolus[131] and the potential for episodes of hypotension in conjunction with the administration of each bolus.[130] We identified 1 observational study[45] and 6 RCTs[130-135] that compared outcomes with intermittent and continuous infusion of epidural analgesia (Table XV). The only observational study was a large retrospective cohort that compared 1630 women receiving intermittent boluses of .25% bupivacaine with 408 women who received continuous infusion of .125% bupivacaine with fentanyl.[45] Use of the intermittent technique was associated was with a somewhat higher rate of cesarean delivery (19% vs 14% continuous; RR, 1.4; 95% CI, 1.0,1.7) but a lower rate of instrumental vaginal delivery (38% vs 44% continuous; RR, 0.9; 95% CI, 0.8, 1.0). Given the large size of the study, both of these differences were statistically significant ($P = .04$). A similar proportion of women in the 2 groups had spontaneous vaginal deliveries (57% intermittent, 58% continuous). However, these findings are confounded by the fact that continuous infusion was more likely to be used when epidural was requested early, making the results difficult to interpret.

Of the 6 randomized trials, 5 reported dose[131-135] and all found that the continuous infusion technique was associated with a higher total dose of local anesthetic. None of the randomized trials found a significant difference in the rate of cesarean delivery between women receiving intermittent and continuous epidurals. Five of the 6 studies[130-133, 135] also found no difference in the use of instrumental vaginal delivery. One study conducted in a nulliparous population[134] found a higher rate of instrumental vaginal delivery with the intermittent technique (66% vs 43% for continuous, $P = .005$). In that study, cesarean deliveries were somewhat lower with the intermittent technique (6% vs 16% continuous), although the differences were not statistically significant. The data also suggest that labors may be somewhat longer with the intermittent technique, although many of the differences were not statistically significant in these relatively small studies.

Fetal outcome was reported by 4 of the RCTs.[130-132, 135] Two studies evaluated FHR patterns because it has been hypothesized that continuous infusion may be beneficial for the fetus because it avoids large fluctuations in levels of local anesthetic[132] and possibly exposure to episodes of hypotension.[130] Lamont et al[130] defined FHR abnormalities as the presence of persistent bradycardia, tachycardia, loss of baseline variability, or recurrent decelerations, and they found that these abnormalities occurred more often when the intermittent technique was used (32% vs 19%; $P = .004$). In contrast, Eddleston et al[132] did not find a higher rate of abnormalities with the intermittent technique. They derived an overall score for the quality of FHR tracings based on baseline rate, variability, and accelerations; the tracings were scored (maximum score = 8) by obstetricians blinded to randomization group (37 intermittent, 38 continuous). The mean scores for the 2 groups were the same (7.8 of 8.0), but women in the continuous infusion group were more likely to have late decelerations lasting at least 10 minutes or until delivery (53% intermittent, 73% continuous; $P = .07$). Although this difference is not statistically significant, it could be because of the relatively small number of subjects in the study.

These studies provide an inconsistent pattern and do not provide any basis for concluding that either method is more often associated with abnormal FHR tracing. However, whatever the effect on the FHR tracing, it is important to note that no study found a difference in Apgar scores for infants of women in the 2 groups.[130-132, 135] In

Table XIV. Randomized controlled trials that compare method of delivery and length of labor for "standard" (0.125% bupivacaine) and "light" (0.0625% bupivacaine + opioid) epidural

Author (y)	#/Group Standard/ Light	All subjects low-risk*	Inductions excluded	Total dose bupivacaine (mg)		% Instrumental deliveries			% Cesarean deliveries		
				Standard	Light	Standard	Light	RR (95% CI)	Standard	Light	RR (95% CI)
Nulliparas											
Chestnut et al[128] (1988)	39/41 †	Y	N	99	67	21	27	.8 (.3, 1.7)	18	15	1.2 (.5, 3.3)
Stoddart et al[44] (1994)	40/38‡	Y	N	138	92	53	42	1.3 (.8, 2.0)	10	8	1.3 (.3, 5.3)
Russell et al[129] (1996)	135/141	N	N	130	95	44	42	1.1 (.8, 1.4)	20	15	1.4 (.8, 2.3)
Multiparas											
Russell et al[129] (1996)	65/58	N	N	117	79	15	24	.6 (.3, 1.3)	14	9	1.6 (.6, 4.5)
Mixed Parity											
Bailey et al[107] (1994)	25/25	N	N	—	—	52	52	1.0 (.6, 1.7)	12	16	.8 (.2, 3.0)

Low-risk, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Epidural stopped in second stage. ‡Opioid in "heavy" and "light" epidural. §Overall length of labor not different.

Table XV. RCTs that compare method of delivery and length of labor for intermittent versus continuous infusion epidural analgesia

Author (y)	#/Group Intermittent/ Continuous	All subjects low-risk*	Inductions excluded	Bupivacaine concentration		Mean total dose bupivacaine (mg)		% Instrumental deliveries		
				Intermittent	Continuous	Intermittent	Continuous	Intermittent	Continuous	RR (95% CI)
Nulliparas										
Bogod et al (1987)	50/50	N	N	.5%	.125%†	130	178	46	52	.9 (.6, 1.3)
Smedstat et al (1998)	29/28	Y	N	.25%	.25%	87	161	24	54	.5 (.2, .9)
Eddleston et al (1992)	40/40	Y	N	.25%‡	.125%†,‡	1.2 mg/kg	1.5 mg/kg	25	38	.7 (.3, 1.3)
Quinn et al (1993)	79/70	Y	N	.375%§	.1%§	97	108	66	43	1.5 (1.1, 2.1)
Mixed Parity										
Hicks et al (1988)	35/38	Y	N	.5%	.075%†	118	135	40	45	0.9 (.5, 1.5)
Lamont et al (1989)	193/188	N	N	.25%	.125%†	—	—	29	32	0.9 (.7, 1.2)

Low-risk, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar. †Bolus top-ups available. ‡Discontinued when fetal head visible. §Both volume of top-ups and rate of infusion decreased beginning at 8-cm dilation.

addition, the 2 studies reporting umbilical cord pH[132, 135] and the 2 examining the need for resuscitation also reported no significant differences between women receiving intermittent and continuous infusion epidural.[130, 135] Overall, there is little evidence for large differences in maternal or infant outcome based on the use of intermittent or continuous infusion epidural.

Combined spinal epidural (CSE) technique. The combined spinal epidural (CSE) technique was introduced for labor analgesia because it combines rapid onset of relief with effective analgesia.[136] A single randomized trial has been performed comparing outcomes with the use of combined spinal epidural technique compared with opioid pain relief.[110] Gambling et al[110] randomized 1223 women to receive CSE or the opioid meperidine. In the overall intention-to-treat analysis, there were no significant differences in the rates of cesarean (6% in both groups) or instrumental vaginal deliveries (8% CSE, 6% meperidine), but the proportion of women with a second stage >2 hours was higher in the CSE group (10% CSE, 4% meperidine). When stratified by parity, the rates of cesarean delivery remained similar for both nulliparous women (10% CSE, 9% meperidine) and multiparous women (3% in both groups).

This trial also raised a concern about fetal well-being with CSE because there were 9 emergency cesarean deliveries for severe bradycardia in the CSE group (1.5%), but none in the meperidine group. All but 1 case occurred in protocol compliant women (ie, women receiving CSE) and all occurred within 60 minutes of the initiation of CSE.

Mean Length of Labor			
1st Stage (hrs)		2nd Stage (min)	
Standard	Light	Standard	Light
5.0	6.4	124	112
§	§	—	—
8.3	8.9	95	100
6.4	6.8	58	66
9.4	10.1	91	65

% Cesarean deliveries			Mean Length of Labor			
		RR	1st stage (h)		2nd stage (min)	
Intermittent	Continuous	(95% CI)	Intermittent	Continuous	Intermittent	Continuous
20	18	1.1 (.5, 2.5)	11.1	9.5	87	106
24	29	0.8 (0.4, 2.0)	—	—	97	93
15	15	1.0 (0.4, 2.8)	9.5	7.0	75	55
6	16	0.4 (0.2, 1.1)	6.3	5.9	72	60
9	18	.5 (.1, 1.7)	—	—	—	—
16	12	1.3 (.8, 2.2)	11.5	11.9	102	90

Although this study was large, methodologic concerns make it difficult to interpret the results. Overall, 35% of women in the CSE group and 42% in the control group did not receive the treatment to which they were assigned. In the meperidine group, 26% of women received CSE and another 12% refused analgesia or delivered so rapidly that use of any analgesia was not possible. Similarly in the CSE group, 13% of women received only meperidine and 15% refused analgesia or had a rapid delivery. Given the high crossover rate, this study would tend to underestimate differences between the groups. There are also concerns about generalizability because the study population was quite young (mean age = 22 years) and not representative of women giving birth in the United States.

The combined spinal-epidural technique has been compared with the epidural technique in 6 randomized trials[136-141] and 3 observational studies[52, 58, 115] (Table XVI). None of the randomized trials found a difference between the 2 techniques in the rate of cesarean delivery. Although 1 of 3 observational studies[52] found a slightly higher rate of cesarean delivery with epidural (OR, 1.5; 95% CI, 1.1, 2.1), the evidence overall strongly suggests there is no difference in the rate of cesarean delivery. Similarly, only 1 of the 6 randomized trials[140] found a significant difference between the techniques in the rate of instrumental vaginal delivery. The only observational study to examine instrumental vaginal delivery also found no difference.[58] No differences were found in length of labor[58, 136] or fetal malposition[58] in the few studies to report these outcomes.

Given the findings of Gambling et al,[110] data regarding fetal outcome in these studies is particularly pertinent. Of the randomized trials, only Van de Velde et al[141] examined fetal outcome. Although they found a slightly higher rate of abnormal FHR changes in the CSE group (36% vs 29%), the difference was not statistically significant (P = .4), and the occurrence of FHR abnormalities in the hour after analgesia was similar (11% CSE, 9% epidural). Palmer et al[115] performed a blind review of FHR monitoring strips for 199 women and found a higher rate of FHR abnormalities (defined as early, late or variable decelerations, or an isolated bradycardia) with CSE compared with epidural (12% vs 6%), although this difference did not reach statistical significance (P = .1). The most specific difference noted was in the rate of isolated bradycardia (5% CSE, 1% epidural). In contrast, Nielson et al,[58] in an observational study of 129 women, found no difference in the rate of FHR abnormalities during the first hour after analgesia for women receiving CSE and epidural (23% in both groups). No study has found a difference in the proportion of women with meconium-stained amniotic fluid[58, 141] or in the mean cord pH values.[58, 115, 141]

Summary: Combined spinal epidural technique. Studies comparing combined spinal-epidural to epidural suggest no difference in the rate of cesarean delivery, the rate of instrumental vaginal delivery, or the length of labor. The unexpectedly high rate of severe fetal bardycardia reported in the only randomized trial of CSE versus opioid pain relief is of concern. Although none of the studies comparing CSE with epidural reported a significant difference in the occurrence of FHR abnormalities, their findings support the possibility of an increase. Further investigation of these findings is warranted.

Newborn Outcomes

Neonatal treatments and procedures. Two studies examined the effect of epidural on neonatal sepsis evaluations and antibiotic treatment. Lieberman et al,[92] in a study of

Table XVI. Method of delivery in studies comparing combined spinal-epidural (CSE) and epidural

Author (y)	*#/Group Epidural/ CSE*	*Population*	*All subjects low-risk**	*Inductions excluded*	*% Instrumental deliveries*			*% Cesarean deliveries*		
					Epidural	*CSE*	*RR (95% CI))*	*Epidural*	*CSE*	*RR (95% CI)*
Randomized trials										
Kartawiadi et al[139] (1996)	31/32	Mixed parity	Y	N	16	22	.7 (.3, 2.1)	6	9	.7 (.1, 3.8)
Nageotte et al[140] (1997)	256/505	Nulliparous	Y	Y	34	26	1.3 (1.1, 1.7)	16	17	.9 (.7, 1.3)
Dunn et al[137] (1998)	34/35	Mixed parity	N	N	6	6	1.0 (.2, 6.9)	12	14	.8 (.2, 2.7)
Dresner et al[138] (1998)	484/524	Mixed parity	N	N	25	26	.9 (.8, 1.2)	22	19	1.1 (.9, 1.5)
Van de Velde et al[141] (1999)	55/55	Mixed parity	N	N	11	13	.9 (.3, 2.4)	5	4	1.5 (.3, 8.6)
Tsen et al[136] (1999)	50/50	Nulliparous	Y	Y	16	16	1.0 (.4, 2.5)	18	16	1.1 (.5, 2.7)
Observational studies										
Nielson et al[58] (1996)	64/60	Mixed parity	Y	Y	23	22	1.1 (.6, 2.1)	14	8	1.8 (.7, 5.2)
Palmer et al[115] (1999)	99/100†	Mixed parity	Y	Y	—	—	—	12	7	1.7 (.7, 4.2)
Traynor et al[52] (2000)	860/424	Nulliparous	Y	N	—	—	—	14	9	1.5 (1.1, 2.1)

**Low-risk*, term, singleton, cephalic. For multiparous subjects, no history previous uterine scar.
†Epidural anesthetic is 0.044% bupivacaine.

1657 term nulliparous women, reported that neonates whose mothers had received epidural analgesia were more likely to be evaluated for sepsis (34.0% vs 9.8%; adjusted OR, 4.3; 95% CI, 3.2, 5.9) and to be treated with antibiotics because of suspicion of sepsis (15.4% vs 3.8%; adjusted OR, 3.9; 95% CI, 2.4, 6.1). The rate of documented neonatal sepsis was low in both groups (0.3% epidural, 0.2% no-epidural). Philip et al[88] (analyzing the RCT data of Sharma et al[18]) also found that newborns of women receiving epidural had a higher rate of sepsis evaluation (25% vs 16%) and a higher rate of antibiotic treatment (19% vs 11%). There were no cases of sepsis in their population.

There are some interesting differences in the findings of these 2 studies. Philip et al[88] found a higher rate of sepsis evaluation with epidural only when the mother became febrile (temperature of at least 38.0°C or 100.4°F), but no association of sepsis evaluation with epidural use when the mother was afebrile (12% epidural, 13% control). This finding is in contrast to Lieberman et al,[92] where infants of afebrile mothers were also more likely to be evaluated (25% vs 9%). Philip et al[88] concluded that the reason for the difference is that their study was randomized. We disagree and believe that the differences result from differences in the criteria for sepsis evaluation between the 2 institutions in which the studies were conducted. Philip et al report that at their institution, in the absence of fever, the criteria for neonatal sepsis evaluation were temperature instability, tachypnea, dusky spells, lethargy, and hypoglycemia. The main factors contributing to an increase in neonatal sepsis evaluation among afebrile women in Lieberman et al were longer rupture of membranes and low-grade fever (99.6°F–100.4°F) during labor.[142] These factors, which occur more frequently with epidural use, would not have prompted neonatal evaluation in the study by Philip et al. Differences in practice guidelines between institutions will influence the rates of both neonatal sepsis evaluation and antibiotic treatment. The standards at Brigham and Women's Hospital (Boston, Mass, where Lieberman et al was conducted) resulted in a higher rate of sepsis evaluation (25% vs 20% in Philip et al) but a lower rate of treatment with antibiotics (11% vs 15% in Philip et al).

Summary: Neonatal treatments and procedures. Both studies examining the association of epidural with neonatal sepsis evaluation found a higher rate among women receiving epidural. This is not unexpected given the well-documented increase in intrapartum fever that occurs with epidural use. Because it is not possible to distinguish infectious from noninfectious fever during labor, infants of febrile mothers are likely to be evaluated. As expected, the magnitude of the association of epidural with sepsis evaluation and antibiotic treatment among afebrile women varies according to institution-specific practice guidelines for performance of evaluations and treatment.

Hyperbilirubinemia. The association of epidural to hyperbilirubinemia was discussed in 7 studies meeting our inclusion criteria (Table XVII).[79, 117, 119, 143-146] All of them found approximately a 1.5- to 2.0-fold increase in the rate of hyperbilirubinemia among babies born to women who had received epidurals. The association reached statistical significance in only 4 of the studies,[143-146] possibly because of the smaller sizes of the other studies.

Although the association between epidural and hyperbilirubinemia is consistent, the reason for the association is not clear. Apart from the epidural itself, 2 other factors have been investigated as possible explanations for the increase, use of oxytocin and instrumental vaginal delivery, both of which may be more likely with epidural analgesia. Instrumental vaginal delivery represents a plausible mechanism because it has been associated with an increase in the occurrence of neonatal jaundice.[145, 147] A role for oxytocin has been suggested by 2 studies report-

Table XVII. Results of studies examining the association of epidural on bilirubin levels in the neonate

			% Hyperbilirubinemia		
Author (y)	*#/Group*	*Definition of hyperbilirubinemia*	*Epidural*	*No epidural*	*OR or RR (95% CI)*
Case control studies	*Hyperbilirubinemia cases/Controls*				
Campbell et al[145] (1975)	312/312	Total serum bilirubin 12 mg/100 mL	55	45	OR, 1.5 (1.1, 2.0)
Sims and Neligan[144] (1975)	46/92	Plasma unconjugated bilirubin >15 mg/100 mL	53	26	OR, 3.6 (1.5, 8.8)
Other studies	*Epidural/No epidural*				
Chalmers et al[146] (1975)	107/10,484	Plasma bilirubin >10 mg/100 mL	16	9	RR, 1.8 (1.1, 2.7)
Willdeck-Lund et al[119] (1979)	178/133	Observation or treatment for jaundice	8	4	RR, 2.1 (.8, 5.7)
Wood et al[143] (1979)	512/178	Plasma bilirubin >12 mg/100 mL	23	12	RR, 1.9 (1.3, 2.9)
Jouppila et al[79] (1983)	43/37	Total bilirubin >15 mg/100 mL	21	14	RR, 1.6 (.6, 4.2)
Sepkoski et al[117] (1992)	20/20	Not defined	15	10	RR, 1.5 (.3, 8.0)

ing that once oxytocin was taken into account, the rate of hyperbilirubinemia did not differ for women with and without epidural,[79, 146] but not all studies confirm these findings.[143] Overall, available data do not permit firm conclusions about the reason for the association of epidural with hyperbilirubinemia.

Retinal hemorrhages. Perinatal retinal hemorrhage has been demonstrated to occur with labor and vaginal delivery but is present only rarely after elective cesarean delivery.[113] The long-term significance of these lesions is not known.[113] We identified 2 studies examining this association.[113, 148] Maltau and Egge,[113] in a small study of 100 term women with spontaneous vaginal deliveries, reported that retinal hemorrhages were significantly less prevalent in the epidural group (56% vs 80% of infants). However, they excluded women with vacuum deliveries, which are likely to be more frequent with epidural and have also been associated with a higher rate of retinal hemorrhages.[149] In a larger study of 976 infants, Van Zundert et al[148] found no difference in retinal hemorrhages in infants with and without epidural analgesia (41% epidural, 43% control). Although there is limited literature, the data suggest that, overall, the rate of retinal hemorrhages in newborns is similar for women receiving and not receiving epidural analgesia.

Neonatal behavioral and neurologic outcomes. We identified 12 studies examining neonatal behavior or neurologic status[17, 29, 39, 112, 114, 117, 118, 150-153] but excluded 1 study from consideration because mothers of some of the control infants received opioids and others did not.[39] Findings from the other 11 studies are summarized in Table XVIII.

All of the studies used 1 of 3 neonatal behavioral assessment tools: the Brazelton Neonatal Behavioral Assessment Scale (NBAS),[154] the Scanlon Early Neonatal Neurobehavioral Scale (ENNS),[155] or the Neurologic and Adaptive Capacity Score (NACS).[156] The NBAS, which takes the longest to administer (30-45 min) and requires significant training to carry out, has been described as the most "comprehensive" neonatal neurobehavioral examination.[157] Analysis of the results of this test often involves aggregation of the data into subscales. The most commonly used subscales examine four dimensions of behavior[158] that have been described as follows:[150]

1. The Interactive Processes subscale assesses the way the baby responds to objects and humans in the environment and includes auditory, visual, and other sensory reception, and the baby's response to these perceptions.
2. The Motoric Processes subscale assesses the reflex and voluntary movements of the baby, including the quality of these movements.
3. The State Control subscale assesses the state the baby is in, ranging from deep sleep to light sleep, wakeful and alert states to agitated fussing and crying states.
4. The Response to Stress subscale assesses how the baby copes with the normal stresses of being undressed, changed, and handled.

The test was designed for use in a clinical setting and is often repeated to chart a baby's progress.

The ENNS was developed by anesthesiologists to examine neurobehavioral changes that occur with anesthetic drugs.[157, 159] The test takes about 10 minutes to perform and is designed to be administered 2 to 8 hours after birth, a period corresponding with the presence of significant levels of drug in neonatal tissue.[157] The ENNS puts more emphasis on tests of muscle tone, reflexes, and decrement in response to stimulation compared with the NBAS, because it was believed that these would be most affected by anesthetic agents.[157] However, it also covers many of the same areas included in the NBAS, including assessment of state and interaction and so provides a general evaluation of the infant.

The NACS was designed to further distinguish details related to neonatal tone, which was thought to be important in differentiating between the effects of birth trauma and drug depression.[157] The test takes <5 minutes to administer. Because both the ENNS and NACS are less comprehensive than the NBAS, it has been suggested that they may fail to detect some effects of drugs.[157] In a recent editorial,[160] the NACS was particularly criticized as an insensitive test.

Table XVIII. Results of studies examining the association of epidural with neonatal behavior and neurologic status

Part 1: Epidural vs no/minimal medication

Author (y)	*#/Group epidural/Control*	*Major evaluation tool*	*Epidural/Drug protocol*	*Age of infant at evaluation*	*Significant findings*
Lieberman et al[112] (1979)	59/35	NBAS	.375% bupivacaine	20 min, 24 hr, days 3,7,21,42	Infants in epidural group less responsive than unmedicated group to the human voice.
Abboud (1982)	3 epidural protocols with 15-21/group; 20 no medication	ENNS	.5% bupivacaine 2% 2-chlorprocaine 1.5% lidocaine	2 and 24 hr	No significant differences between any epidural group and the no medication group.
Abboud (1983)	22/17	ENNS	1.5% lidocaine	2 and 24 hr	No significant differences between groups.
Abboud (1984)	3 epidural protocols with 19-23/group; 19 no medication	NACS	.5% bupivacaine 2% 2-chlorprocaine 1.5% lidocaine	2 and 24 hr	No significant differences between any epidural group and the no medication group.
Murray et al[114] (1981)	40/15	NBAS	.25% bupivacaine Brief nitrous oxide by some in no med group; local lidocaine infiltration	Days 1, 5 and 1 month	Epidural associated with lower scores overall at day 1 with differences in motoric processes, response to stress and state control. Differences remained at day 5 but not at 1 month.
Sepkoski et al[117] (1992)	20/20	NBAS	—	3 hr, and days 3, 7 and 28	Epidural associated with lower scores on orientation and motor clusters; dose response noted.

Part 2: Epidural vs parenteral administration of opioids

Wiener et al[118] (1979)	11/18	ENNS	.5% bupivacaine	.5, 4, 8, 12, 24, 48 hr	Epidural group habituated to sound more quickly. Epidural group with poorer muscle tone.
	11/15	ENNS	.375% bupivacaine Opioid reversed by naloxone HCl	.5, 4, 8, 12, 24, 48 hr	Epidural group had decreased reflexes. Epidural group with poorer muscle tone.
Lieberman et al[112] (1979)	59/51	NBAS	.375% bupivacaine Some nitrous oxide in both groups	20 min, 24 hr, days 3, 7, 21, 42	No significant differences between groups.
Kangas-Saarela et al[150] (1987)	14/15	ENNS	.5% bupivacaine Epidural group also received opioid	3 hr; 1, 2 and 4 or 5 days	Epidural infants habituated to sound and oriented to inanimate sound better.
Thorp et al[17] (1993)	48/45	NACS	.125% bupivacaine	2 and 24 hr	No significant differences between groups.
Nikkola et al[29] (1997)	10/10*	NACS	.375% bupivacaine	1 and 13 hr	No significant differences between groups.

*40% crossover rate from no epidural to epidural.

All of the studies we reviewed were conducted in low-risk populations. Two were RCTs conducted in term nulliparous women and their newborns.[17, 29] The remaining studies included only women with term pregnancies and vaginal births. Virtually all the studies examined infant behavior within the first 4 to 6 weeks, with most of the assessments conducted during the infants' first 48 hours of life. Infants exposed to epidurals were compared with either infants exposed to opioids or with infants whose mothers were not medicated during labor. Some studies were limited to infants who had normal Apgar scores or a normal umbilical cord pH.[118, 150] Because these studies were limited to infants who were healthy at birth, any potentially negative outcomes associated with either epidural or opioid that influence neonatal status at birth (eg, by causing low Apgar scores) are hidden. The studies are grouped according to the exposure of the control group (ie, opioid or no medication).

Comparisons with nonmedicated infants. Six studies compared neurobehavioral outcome in infants of women who received epidurals with infants whose mothers received no medication or minimal medication during labor.[112, 114, 117, 151-153] Three of these studies were conducted by a single group of investigators (Abboud et al) who used the ENNS test for 2 studies[152, 153] and the NACS test for the other.[151] None of these 3 studies found any differences between the epidural-exposed and the nonmedicated groups of infants. The remaining studies used the NBAS examination,[112, 114, 117] and all 3 found significant differences between the groups. Lieberman et al[112] identified the fewest significant differences between the groups, finding only that epidural-exposed infants were less responsive to the human voice in the delivery room. Murray et al[114] compared 40 epidural-exposed babies with 15 nonmedicated controls and found a lower overall mean NBAS score at 1 and 5 days for infants exposed to epidural. Significant differences were found for the motoric processes, response to stress, and state control scales on day one. The largest differences were in the state control scale; only 13% of the nonmedicated infants had poor state control compared with 50% of the epidural-exposed infants. The differences remained when controlling for the confounding effect of forceps deliveries, but no dose-response effect was found. By day 5, only the state control scale remained significantly different, and at 1 month, there were no differences in NBAS test results between the groups. However, at 1

month of age, the mothers of epidural-exposed babies viewed their infants less favorably in general and found them more difficult to care for.

Sepkowski et al[117] used the NBAS to compare 20 epidural-exposed infants with 20 nonmedicated infants matched for potentially confounding factors, including maternal ponderal index, parity, the number of maternal and fetal nonoptimal conditions, and induction of labor.[161] The epidural-exposed infants showed less alertness and ability to orient during the first month of life and were less mature in motor function. Multivariate analysis examining the dose of bupivacaine demonstrated a dose response for both the orientation and motor effects.

It is not clear why some studies have found differences associated with exposure to epidurals, whereas others have not. Because these are tests of behavior, the examiner may be important. All examiners were blinded to infants' exposure. Some (but not all) of the differences in findings could be related to the tests chosen for evaluation, if the tests indeed differ in their sensitivity. All of the 3 studies comparing epidural-exposed and nonmedicated infants using the NBAS found some differences in outcome, although the differences were much greater in 2 of the studies,[114, 117] both of which found poorer motor function in epidural-exposed infants. The analyses in both of these studies were sophisticated and controlled for a variety of potential confounding factors.

The interpretation of these findings is complex. Early differences in infant behavior might be attributable to a direct effect of the medication on the infant.[114, 117] Such an explanation would be supported by the presence of a dose-response effect, which only 1 of the studies was able to demonstrate.[117] However, differences up to 1 month later cannot be attributed to a direct effect of drugs. Brazelton[154] hypothesized that early interactions with a baby who is less alert, less able to orient, and less able to show organized movements may interfere with the development of the mother-infant relationship.[114, 117] Alternatively, differences in maternal behavior could relate to maternal personality characteristics that influenced both her choice of pain relief in labor and her interactions with her child. It is not possible to rule out this alternative explanation, although Murray et al[114] believe that this alternative is unlikely because mothers in the 2 groups did not differ on a test of caregiving attitudes[162] administered within 24 hours of giving birth.

Comparisons with opioid-exposed infants. Comparisons of epidural-exposed and opioid-exposed infants are of great practical importance because many women who do not receive epidurals choose to receive opioids. Five studies compared infants whose mothers had received an epidural with infants whose mothers had received opioids.[17,29,112,118,150] Two of these studies, Thorp et al[17] and Nikkola et al,[29] were RCTs. Both studies used the NACS test to evaluate the infants, and neither found any differences between the groups. However, Nikkola et al was a very small trial (n = 20), and 40% of the women randomized to the no-epidural group actually received epidural. In Thorp et al, the concentration of bupivacaine administered was lower than in the other trials (.125%), although it is not known if this contributed to their failure to detect differences.

Wiener et al[118] performed 2 separate comparisons using the ENNS. In one, they compared 11 epidural-exposed infants to 18 opioid-exposed infants and found that the epidural group had better habituation to sound but poorer muscle tone. In the second part of their study, they compared epidural exposed infants with opioid-exposed infants who had received naloxone HCl to reverse the effects of their opioid exposure and found no difference in habituation to sound but an even larger difference in muscle tone between the groups. When compared with the opioid-naloxone HCl group, the epidural group also demonstrated decreased reflexes. Kangas-Saarela et al[150] also used the ENNS to compare epidural- and opioid-exposed infants. Similar to Wiener et al, they found that epidural-exposed infants oriented better to inanimate auditory stimuli and habituated better to sound compared with opioid-exposed infants. Lieberman et al[112] evaluated 59 epidural-exposed and 51 opioid-exposed infants using the NBAS and found no differences between the 2 groups.

As a whole, the studies comparing epidural-exposed infants with opioid-exposed infants did not find large differences or consistently better performance by 1 group. Epidural-exposed infants tended to perform better on auditory orientation and habituation, whereas opioid-exposed infants had better muscle tone. One study suggests that opioid-exposed infants treated with naloxone HCl may perform better than opioid-exposed infants not receiving naloxone HCl.

Breast-feeding. The relationship between breast-feeding and epidural has not been widely studied, and we found only 2 studies that addressed it specifically. Kiehl et al[163] found that among 100 privately insured women breast-feeding at discharge, those who had received epidural were less likely to still be breast-feeding at 6 months postpartum (30% vs 50%; $P = .04$). However, the results are somewhat difficult to interpret because the authors failed to provide information on medications during labor in the women who did not receive epidurals and other differences in characteristics that may confound the association between epidural and breast-feeding. Loss to follow-up among the nonprivately insured patients was too great (55%) to allow meaningful interpretation. Halpern et al[164] conducted a prospective study of 189 women to compare breast-feeding among women who received epidural and women who received opioid for pain relief during labor. The study was conducted in a population of middle-class women in a setting with an extraordinarily high rate of breast-feeding suc-

cess and maintenance (93% of the study population with full or partial breast-feeding at 6 weeks). In a logistic regression model controlling for confounding factors, they evaluated each of the specific drugs used for labor analgesia and found that none predicted difficulty in initiating breast-feeding or level of breast-feeding at 6 to 8 weeks postpartum.[164]

The results of this study are difficult to interpret because the authors never present the actual number of women with difficulty initiating breast-feeding according to whether epidural or opioids were used during labor. More important, it does not seem useful to study predictors of breast-feeding continuation to 6 to 8 weeks postpartum in a population where 93% of women are still breast-feeding at that time. Because almost all women were still breast-feeding at 6 to 8 weeks, the outcome chosen for evaluation was level of breast-feeding (categorized as full, partial, or token), an outcome that is likely to be related strongly to lifestyle choices, such as the need to return to work.

In addition, comparability of breast-feeding success of women receiving epidural and women receiving opioid does not necessarily imply that labor analgesia does not influence breast-feeding success. It is also possible that opioid and epidural have similar effects on breast-feeding, since as noted by Halpern et al,[164] there is literature to suggest an adverse effect of opioids on initiation and maintenance of breast-feeding. Given these questions, and the limited availability of data, there is clearly a need for further research examining the effects of both epidural and opioid on breast-feeding success.

Neonatal outcomes and epidural-related fever. Epidurals are associated with a higher rate of maternal fever during labor. Though this fever is unlikely to be of infectious origin, it may still be of significant concern. When maternal temperature is increased, the temperature of the fetus rises too. In primate studies, hyperthermia in the absence of infection has been directly associated with the development of fetal hypoxia, metabolic acidosis and hypotension.[165] Other animal studies have demonstrated that an increase in brain temperature of even 1 or 2°C increases the degree of brain damage resulting from an ischemic insult.[166-168] Among adults admitted with stroke, higher body temperature at admission has been associated with an increase in stroke severity, infarct size, and mortality.[169] These findings suggest that maternal intrapartum fever could be injurious to the fetus by increasing the risk of neurologic injury independent of infection. In addition, fetal temperature may reach high levels more often than indicated by maternal temperature, because studies in humans indicate that fetal temperature is 0.5°C to 0.9°C higher than maternal temperature.[165, 170-174] Because only about 15% of women receiving epidurals have a fever, adverse outcomes that occur only in the presence of intrapartum fever would unlikely be detected in studies examining the effect of epidural overall. For example, if an adverse event occurs at a rate of 3% among women not receiving epidural and afebrile women who receive epidural, a tripling (to 9%) among febrile women in the epidural group would only raise the overall rate of the adverse event to 3.9% in the epidural group. A study of at least 13,000 women would be needed to detect the difference between 3% and 3.9%. In contrast, a study directly comparing rates in febrile (3%) and afebrile (9%) women requires a study size of only 500 women.

We identified only 2 articles comparing febrile and afebrile women in term low-risk populations.[175,176] Lieberman et al[175] examined the association of fever with neonatal outcome in 1218 nulliparas with singleton term pregnancies and spontaneous onset of labor. Ninety-eight percent of febrile women had received an epidural. Infants of women developing fever >100.4°F were 3 times more likely to have 1-minute Apgar scores <7 (22.8% vs 8.0%; $P < .0001$) and 10 times more likely to be hypotonic after delivery (4.8% vs 0.5%; $P < .0001$). Compared with infants of afebrile women, infants whose mothers' maximum temperatures were >101°F were 4 times more likely to require bag and mask resuscitation (11.5% vs 3.0%; $P = .0004$), and 6 times more likely to be given oxygen therapy in the nursery (8.2% vs 1.3%; $P = .002$). The study also reports a higher rate of neonatal seizures among infants of women whose fever was >101°F (3.3% vs 0.2% for afebrile; $P = .015$). The authors caution, however, that although the relative increase was large and the finding was statistically significant, the result should be regarded as preliminary because it was based on a small number of cases (n = 4). All associations remained essentially the same after controlling for confounding factors in logistic regression analyses.

The same authors subsequently conducted a case-control study examining the association of fever with unexplained seizures in term infants.[176] Cases included all term infants with unexplained neonatal seizures born to women who labored. Infants were excluded if there was a diagnosis of neonatal infection or if there was another identifiable proximal cause for the seizure, such as central nervous system anomalies, skull trauma, or a metabolic disease. Four singleton, term controls with a trial of labor were selected for each of the 38 cases identified, matched by date of birth and parity, for a total of 152 controls. Overall, 31.6% of the cases, but only 9.2% of the controls ($P = .001$), were exposed to intrapartum fever. Mothers of infants who had seizure were not more likely to have other signs, suggesting infection such as premature rupture of the membranes or a high white blood cell count at admission. When controlling for other labor events associated with seizures, the association of intrapartum fever with unexplained seizures remained (OR, 3.4; 95% CI, 1.03,10.9).

Summary: Fever related outcomes. There is currently only a modest amount of data investigating the association of

epidural-related fever with adverse neonatal outcomes. With the exception of seizures, all of the adverse events that have been noted were transient. The finding of a possible association with seizure is of greater concern.

Seizure represents the best predictor of later neurologic damage in the term infant.[177] Although previous studies have reported an association of intrapartum fever with adverse neurologic outcome, those studies have viewed fever exclusively as a marker for an infection that was responsible for the adverse outcome. For example, Adamson et al[178] reported that intrapartum maternal fever is a risk factor for neonatal encephalopathy among term infants, but they hypothesized that the association was related to the presence of sepsis. Similarly, in a recent study, Grether and Nelson[179] suggested that maternal infection during labor might represent a risk factor for cerebral palsy among term infants. However, in that study, fever >100.4°°F was sufficient for a woman to be classified as infected. Because the manifestations of the febrile response are similar regardless of whether the causative agent is infectious or noninfectious,[180] it is possible that these previously reported associations reflect physiologic changes that are related to fever independent of infection.

Additional studies, particularly randomized trials, examining these outcomes are needed. Although seizures cannot be studied in a randomized fashion (because they are rare events) the finding of other adverse neurologic outcomes (such as hypotonia) in randomized trials would increase concern.

Maternal Postpartum Effects

Postpartum hemorrhage and retained placenta. Two articles consider the issue of postpartum hemorrhage.[116, 181] One compared outcomes from a large number of deliveries at 2 university teaching hospitals in Australia.[181] The authors reported very different associations of epidural with postpartum hemorrhage in the 2 institutions. At one hospital, they found no difference in the rate of postpartum hemorrhage for women receiving and not receiving epidural analgesia (4% in both groups), whereas there was a very large difference in postpartum hemorrhage in the other hospital (15% epidural, 3% no epidural; RR, 5.6; 95% CI, 4.7, 6.6). No multivariate analyses were performed. The other study examining this association[116] was conducted in England and examined more than 25,000 term women with singleton pregnancies and spontaneous onset of labor. The rate of postpartum hemorrhage was twice as high among women who received epidurals (10% vs 5%; RR, 1.9; 95% CI, 1.7, 2.1). The association remained in sophisticated multivariate modeling that controlled for other maternal and labor characteristics.

The reasons for the difference in the reported associations are unclear. One difference between the institutions is the rate of epidural use in the overall population. At the 2 institutions where epidural use was associated with postpartum hemorrhage, the overall rate of epidural use was relatively low (8%[181] and 15%[116]), whereas epidurals were used by 40% of women giving birth at the institution where no association was apparent.[181] One possible explanation is that the association occurred because the women who received epidurals at the hospital with the low overall use of epidurals were at higher risk of postpartum hemorrhage because of medical conditions not controlled in the analysis. Further study will be needed to determine whether a true association exists.

Only 1 study has examined the association of epidural with retained placenta.[181] St George and Crandon[181] examined all 75 cases of retained placenta in a population of 4998 women delivering and compared these cases with 152 controls. Although approximately one third of the cases also had postpartum hemorrhage, in this population postpartum hemorrhage was not associated with epidural use. There was a significantly higher rate of epidural use among the women with retained placenta (51% vs 32%; RR, 2.2; 95% CI, 1.2, 4.1). Confounding factors were not controlled. Given this very limited data, it is not possible to draw conclusions. Further study is needed.

Urinary retention and stress incontinence. Urinary retention is a known complication of childbirth. The first study to examine epidural as a possible risk factor for urinary retention[182] suggested that epidural analgesia could delay normal voiding by reducing or suppressing afferent sensory impulses from the bladder, thereby inhibiting the reflex mechanism that normally induces micturition.[183] Two slightly different outcomes have been investigated (Table XIX). The first is symptomatic urinary retention requiring treatment. Kermans et al[184] found a significant increase in the rate of urinary retention among women who had received epidural analgesia (4% vs 1%) as did Olofsson et al[185] (2.7% vs .1%). Both studies were relatively large and in both, 1% to 2% of women were found to have this complication. However, despite the consistency of these results, their interpretation is unclear. One explanation for the findings is that epidural is directly or indirectly responsible for urinary retention. An indirect association could occur if an outcome associated with epidural (such as long labor or instrumental vaginal delivery) causes urinary retention. Neither study controlled for confounding factors, however, and it is possible that uncontrolled confounding factors could also explain these results. For example, because nulliparas are more likely to have urinary retention and are also more likely to receive epidural, if nulliparity is the actual culprit, failure to control for this factor could create a false association.

Several studies have also investigated asymptomatic urinary retention, generally defined as a high residual volume in the bladder after voiding. The 4 studies examining this issue have yielded conflicting results.[182, 186-188] Two studies, Ramsay and Torbet[188] and Andolf et al,[186] found positive associations between epidural use and urinary retention,

Table XIX. Results of studies examining the association of epidural and urinary retention

Author (y)	#Epidural/ # No-epidural	Population	Measures of retention	% Urinary retention		
				Epidural	No Epidural	RR (95% CI)
Symptomatic						
Kermans et al[184] (1986)	312/539	Mixed parity	Absence of micturition within 6 hr of vaginal delivery or >6 hr after catheter removal for cesarean delivery	4	1	3.0 (1.2, 7.4)
Olofsson et al[185] (1997)	1000/2364	Mixed parity	Unable to void spontaneously with >500 mL residual volume on catheterization	3	.1	21.3 (6.5, 70.0)
Asymptomatic						
Weil et al[182] (1983)	11/11	Nulliparas, vaginal delivery	Residual volume >100 mL after void	18	18	1.0 (.7, 5.9)
Ramsay and Torbet[188] (1993)	54/94	Mixed parity, spontaneous vaginal delivery	Residual volume >100 mL or mean urinary flow rate <10 mL/sec	50	27	1.8 (1.2, 2.8)
Andolf et al[186] (1994)	95/444	Mixed parity, spontaneous vaginal delivery	Residual volume >150 mL after void	4	1	4.7 (1.2, 18.4)
Weissman et al (1995)	68/38	Mixed parity, vaginal delivery	Residual volume >100 mL after void	13	11	.9 (.4, 2.0)

*40% crossover rate from no-epidural to epidural.

whereas 2 other studies, Weil et al[182] and Weissman et al,[187] found no association. The reason for the difference in findings from these studies is unclear. None of these studies controlled for potential confounding factors and because confounding may be present by parity, perineal lacerations and instrumental vaginal delivery, the presence or absence of an association cannot be determined.

The 2 studies evaluating the association of stress incontinence and epidural also report conflicting results. In both studies, information about stress incontinence was obtained by interview with the mother between 6 and 12 weeks postpartum. Dimpfl et al[189] did 2 separate surveys comparing the rate of stress incontinence for epidural analgesia and pudendal block. Both surveys found a lower rate of stress incontinence among women who received epidural. The first study, which included all healthy women delivering (n = 276), found a significant protective effect of epidural on stress incontinence (1% epidural, 9% pudendal; RR, .1; 95% CI, .02, .9). The second survey, which included only primiparous women (n = 180), also found a lower rate of stress incontinence with epidural (4% vs 9%), although the association did not reach statistical significance (RR, .5; 95% CI, .2, 1.7). In contrast, Viktrup et al,[190] in a study of 200 nulliparous women, reported a significant increase in the risk of stress urinary incontinence among women who had received epidural after delivery (27% vs 13%; RR, 2.1; 95% CI, 1.1, 3.9) and at 3 months postpartum (16% vs 4%; RR, 4.2; 95% CI, 1.5, 12.0). At 1 year postpartum, the proportion of women with stress incontinence remained somewhat higher in women who had received epidural (7% vs 3%), but the difference did not reach statistical significance ($P = .2$). In that study, approximately half of the women not receiving epidural had received a pudendal block. The explanation for the difference in results of the 2 studies is unclear.

It is not possible to determine from available data whether epidural increases the risk of urinary retention or influences the rate of stress incontinence. Further investigation is needed.

Backache. Six studies discussing back pain and epidural meeting our inclusion criteria were identified.[15,59,191-196] Two of them presented results on the same population, so only one was included. Findings from the 5 studies we included are presented in Table XX.

One randomized trial examined the association of epidural with backache in low-risk, nulliparous women delivering at term.[15] In an intention-to-treat analysis, they found no significant difference in the occurrence of middle- or low-back ache at 3 months and 12 months postpartum. However, interpretation of the results is complicated because approximately 30% of women in each randomized group did not receive the treatment to which they were assigned.

Of the 4 observational studies, only Macarthur et al[195] found women receiving epidural to be at a significantly increased risk for new, long-term backache compared with women not receiving epidural (19% vs 11%; RR, 1.9; 95% CI, 1.7, 2.0). Interpretation of this study is particularly problematic because women were asked to recall events related to deliveries that were 2 to 9 years before the survey. In addition, there was a very low response rate (39%). Macarthur et al subsequently published 2 other studies reporting shorter- and longer-term outcomes on a single cohort of women.[192,193] In the first study,[192] they found an increase in back pain on the first day postpartum, but the difference was no longer significant at 7 days or 6 weeks postpartum. In a logistic regression adjusting for confounding factors, they reported an adjusted OR of 2.2 (95% CI, .9-5.5) for the association of epidural with back pain at 6 weeks postpartum. The study excluded women with back pain before pregnancy, and further exclusion of women who developed back pain during pregnancy did not alter the results. A follow-up of the same population at 1 year postpartum (with a 74% response rate) indicated that there was no increase in long-term

Table XX. Results of studies examining the association of epidural with maternal back pain

Author (y)	*#/Group epidural/ No epidural*	*Subjects limited to low-risk**	*Data collection method*	*Definition of back pain*	*% with back pain*		
					Epidural	*No Epidural*	*RR (95% CI)*
Howell et al[15] (2001)	184/185	Y	Randomized trial; follow-up questionnaire	Self-report at 3 and 12 mo postpartum	Low backache# 35	27	1.3 (.9, 1.8)
					Middle backache 16	16	1.0 (.6, 1.6)
Macarthur et al[195] (1990)	4340/6591	N†	Postal questionnaires	New back pain beginning within 3 months of delivery, lasting at least 6 wk	19	11	1.9 (1.7, 2.0)
Macarthur et al[192] (I) (1995)	164/165	Y	Interview, conducted by nurse blind to study hypothesis	Self-report of back pain at days 1 and 7 and 6 wk postpartum	53	43	1.5 (1.0, 1.6)‡
(II)					21	23	.9 (.6, 1.4)§
(III)					14	7	1.9(1.0, 3.7)‖
Russell et al[59] (1996)	319/131	N	Interview and postal questionnaire	Self-reported symptoms of new back ache at 3 mo postpartum	8	7	1.1 (.9, 2.3)
Macarthur et al[193] (1997)	121/123¶	N	Telephone interview and questionnaire	Same as Macarthur 1995, but interviewed at one y postpartum	10	14	.7 (.4, 1.4)

*Term singleton, cephalic presentation, no previous uterine scar. Also, no previous history of back pain. †Similar results when subjects with vaginal delivery or spontaneous vaginal delivery evaluated. ‡Analysis I: day 1 postpartum. §Analysis II: day 7 postpartum. ‖Analysis III: 6 weeks postpartum. ¶Same study population as Macarthur (1995), less the subjects lost to follow-up. #Data presented for 12 month follow-up; no difference between groups at 3 month follow-up.

backache associated with epidural use (adjusted OR, .63; 95% CI, .3, 1.6). Similarly, in a follow-up of patients at three months postpartum (75% response rate), Russell et al[59] found no difference in the rate of new backache among related to epidural use.

The ascertainment of outcome in these studies was uniformly based on self-report. However, if recall bias were important, one would expect women who had received epidural to report a higher rate of backache, because at least 1 study published in 1987 indicated that women in the United Kingdom believed epidural to be a risk factor for backache.[197] (The studies of Macarthur et al[195] were conducted in Canada and those of Russell et al in London). Current data do not support an association between the use of epidural and development of new, long-term backache in women.

Comments

This review examined the state of our knowledge regarding the association of epidural with a variety of maternal, fetal, and neonatal outcomes. For many of these outcomes, we found considerable variation in their association with epidural use. This is to be expected because the associations being examined are complex and influenced by many factors. In addition, some of the outcomes examined, such as fever, are primarily physiologic, whereas others, such as cesarean delivery, although influenced by physiology, are in the end practices determined by the care provider. Even in the absence of epidural, cesarean delivery rates vary dramatically from institution to institution and within institutions, from provider to provider.[198] The influence of epidural on obstetric management is also likely to vary. Some physicians may be more likely to intervene early when labor fails to progress, whereas others may choose to wait. Some physicians tend to manage inadequate progress in the second stage with forceps or vacuum, whereas others may perform a cesarean delivery. Because of variation in practice, greater variability is expected in the association between epidural, and any outcome that is strongly practice-based.

Our review revealed that despite the large number of studies that have been conducted, there is much we do not know about the effects of epidural on mother and fetus. Additional research is clearly needed to rectify this deficit, especially with regard to the effects of maternal temperature elevation on the fetus. The specific areas needing further research are noted in the review. There is a particular need for additional, well-conducted randomized trials. It is strongly preferable that studies comparing epidural with other forms of pain relief randomize women during pregnancy so participants are more representative in terms of the difficulty of their labors. This design would greatly enhance the generalizability of study findings.

In addition to demonstrating where further research is needed, this review also reveals that there are some unintended effects that consistently accompany epidural use. These unintended effects are present in randomized trials as well as observational studies. We are obligated to inform women about these side effects so they can make truly informed decisions about the use of pain relief during labor. Information about choices for pain relief during labor needs to be conveyed during pregnancy; once women are in labor, it is too late. This obligation is particularly pressing because use of epidural for pain relief during labor is an elective procedure.

Nulliparous women should be told that they are less likely to have a spontaneous vaginal delivery, that they are more likely to have an instrumental vaginal delivery, and that their labor is likely to be longer. They should also be informed of the implications of the higher rate of instrumental vaginal delivery, specifically the increased rate of serious perineal lacerations that accompany its use. Women should also be informed of the higher rate of intrapartum fever. They should be informed that if they develop a fever their infant may be more likely to be evaluated for sepsis and treated with antibiotics for suspected sepsis but that there is no evidence that epidural increases infection in mothers or infants. Issues addressed in informed consent will need to be modified as we learn more.

Epidural analgesia represents one of a spectrum of options for pain relief during labor that should be available to women. In addition to continuing research related to epidural, research into other pharmacologic and nonpharmacologic methods of pain relief should also continue.

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