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REVIEW ARTICLE

Labour analgesia and the baby: good news is no news

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ABSTRACT
When investigating different methods of maternal pain relief in labour, neonatal outcome has not always been at the forefront, or else maternal changes, such as haemodynamics, fever, length of labour, need for oxytocin or type of delivery, are taken as surrogates for neonatal outcome. It is essential to examine the actual baby and to appreciate that labour pain itself has adverse consequences for the baby. For systemic analgesia, pethidine has been most extensively studied and compared with neuraxial analgesia. It depresses fetal muscular activity, aortic blood flow, short-term heart rate variability and oxygen saturation. In the newborn it exacerbates acidosis, depresses Apgar scores, respiration, neurobehavioural score, muscle tone and suckling. Alternatives have few advantages, remifentanil being the most promising. Neuraxial analgesia is associated with better Apgar scores and variable neurobehavioural changes. Neonatal acid-base status is not only better with epidural than with systemic opioid analgesia, it is also better than with no analgesia. The effect on breast feeding has yet to be established, though it is certainly no worse than that of systemic opioid analgesia. Variations in neuraxial technique have little impact on the newborn. Widespread ignorance of the benefit to the newborn of neuraxial labour analgesia in the UK among non-anaesthetists needs to be combated.

Keywords: Labour analgesia; Fetal effects; Neonatal outcome; Umbilical artery acid-base

Introduction

It is widely assumed among the lay, and indeed by many healthcare workers, that any pharmacological form of analgesia must have adverse effects on the baby, and that neuraxial analgesia, being the most invasive form, must be the most harmful, while unmodified labour is relatively harmless. All these assumptions must be questioned. Further misleading information is promulgated by assuming known maternal complications of neuraxial analgesia to be valid surrogates for neonatal outcome, with little evidence of a direct link. It is not disputed that neuraxial analgesia may cause maternal hypotension and fever, may prolong the second stage and increase the need for oxytocin administration and instrumental delivery. These maternal changes may lead one to suppose neuraxial must be the worst type of analgesia for the baby, but they *cannot be used as surrogates for neonatal outcome.* Other effects that may be beneficial are overlooked and neonatal outcome depends on the balance of these opposing forces.

Obstetric anaesthetists must be fully conversant with all the conflicting facts, because if we are not, how can we expect others to understand them? To this end, I want to lay out the evidence relating to the baby, because the unfavourable maternal effects receive disproportionate exposure. I include some elderly references, as they demonstrate how long ago the favourable effects of epidural analgesia on the baby were demonstrated, and how consistent they are, but how little attention has been paid to them.

In the UK we meet opposition to epidural analgesia in labour. Prominent midwives are concerned that *almost one in five women now receive an epidural during labour* (big deal!), and urge their colleagues to warn women of all the dreadful complications. As these are the people most likely to inform mothers about pain relief in labour, no wonder we meet with resistance.

Of the patient information resources that I have seen, only one explains the neonatal benefits, as well as the maternal complications, of neuraxial analgesia in labour.[1] There was a second, but the neonatal benefits have since been glossed over.[2] I believe that opposition to the Obstetric Anaesthetists' Association leaflet has been sparked in some quarters not only because it said there was little evidence for the efficacy of some alternative methods of analgesia and gave some awkward facts about pethidine, but also because it once claimed neonatal benefit from epidural analgesia.

Alas, no longer. Aren't we missing a trick?

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The effects on mother and baby of labour pain

It has long been known that painful labour produces several adverse changes in maternal physiology and biochemistry, which are ably summarised by Loo and Irestedt.[3] Some changes have important implications for the baby.

Maternal respiration increases by 75–150% during the first stage of unmodified labour;[4] this is associated with a number of maternal changes that may have adverse fetal effects:[4–16]

- Hypocarbia and a respiratory alkalosis.
- Increased oxygen consumption.[4,5]
- Under-ventilation between contractions, resulting in episodes of haemoglobin desaturation, which are more pronounced when systemic opioids are given.[9]
- Compensatory metabolic acidosis, which appears to be transferred readily to the fetus.[10–13]
- Vasoconstriction, which affects the uterine arteries.[14,15]
- A shift in the maternal oxygen dissociation curve, counteracting the double Bohr effect. Many years ago it was demonstrated in sheep that maternal hyperventilation resulted in reduced oxygen content in umbilical venous blood, while restoring the carbon dioxide to a normal level reversed this phenomenon.[15] Adverse effects of hypocarbia seemed at first harder to demonstrate in humans.[6] Nevertheless, a reversal of these phenomena would help to explain the reduction in metabolic acidosis and other favourable effects that are actually seen with neuraxial analgesia (see below).
- Maternal hyperventilation lowers the umbilical artery PCO_2 but as labour progresses this change is overtaken by metabolic acidosis of increasing severity, such that the longer the second stage of labour, the lower the cord pH at birth.[12]

Maternal pain and stress have adverse fetal effects. Maternal anxiety is associated with increased plasma catecholamines and cortisol, and prolonged labour.[17–20] Painful labour activates the stress response, with release of ACTH and β lipotropin, hence cortisol and β endorphin, though the latter fails to exert much analgesic effect. Increased sympathoadrenal activity may lead to incoordinate uterine action and reduced uteroplacental perfusion.[3] The metabolic outcome is hyperglycaemia with a poor insulin response, lipolysis with increased free fatty acids, ketones and lactate. Such acids cross the placenta and together with catecholamines, increase fetal oxygen requirement, so maternal metabolic acidosis from this further cause is compounded in the baby.

While the maternal stress response is somewhat counterproductive, it can be suppressed by neuraxial analgesia (see *Neuraxial analgesia*). By contrast the fetal stress response to labour, which results in a conspicuous catecholamine surge, is beneficial for adaptation to extrauterine life and is *not* suppressed by maternal neuraxial analgesia.[21,22] A double unwhammy for epidurals!

The ways in which maternal analgesia may affect the baby

Drugs given to a mother during labour may affect the baby either after placental transfer (*direct* effects) or via effects on maternal physiology and biochemistry (*indirect* effects). Clearly the former mechanism is potentially important for drugs that act systemically, while neuraxial analgesia does not depend for its effect on the presence of drug in maternal blood, so placental drug transfer is less relevant, while indirect effects may be more prominent.

Placental drug transfer[23]

Drugs used for anaesthesia and analgesia cross the placenta by passive diffusion; in this respect the placenta behaves like other lipid membranes, allowing lipophilic particles to cross readily up to a molecular weight of 600–1000 (i.e. most drugs but not the moiety bound to plasma proteins) and polar substances only up to 60–100. Therefore drugs used to provide systemic and regional analgesia cross the placenta readily in the unbound and non-ionised state, while hydrophilic substances such as neuromuscular blocking drugs diffuse across only slowly and are unlikely to attain effective concentration in the fetus.

The transplacental distribution of lipophilic substances, whose unbound and non-ionised moiety equilibrates readily across the placental membrane, is influenced by the transplacental gradient for pH and binding protein. As fetal plasma pH is lower than maternal, free base tends to concentrate on the fetal side due to ion trapping, the reverse being true for weak acids. This increases the exposure of the acidotic fetus to basic drugs such as opioid analgesics and local anaesthetics.

Acidic drugs are bound mainly to albumin, which shows little transplacental gradient. For most basic drugs, the principle binding protein is α_1-acid glycoprotein, the concentration of which is always much lower in fetal than maternal plasma.[24] For drugs mainly bound to α_1-acid glycoprotein, therefore, higher maternal than fetal binding reduces the equilibrium fetal/maternal ratio.

Although diffusion is no bar to transfer of lipophilic drugs, the fetal compartment is deep, and equilibration takes longer in fetal than maternal tissues. Fetal exposure is therefore dependent on blood flow on either side of the placenta (flow-dependent transfer), equilibrium ratios and duration of maternal exposure.

Although immediate drug effect is related to the concentration of the free moiety, a large albumin-bound component represents a storehouse to the newborn. Albumin binding moreover tends to decline in the first postnatal days, so increasing the free concentrations of drugs such as fentanyl and diazepam.[25]

Systemic analgesia

The main purpose of this review is to address effects on the baby of neuraxial analgesia, but a brief overview of systemic analgesia is needed for balance. Systemic analgesia depends upon the presence in maternal blood of an effective concentration of drug, while any substance that can affect the maternal central nervous system must cross the blood-brain barrier hence also the placenta. Therefore this approach is likely, given time, to affect the fetus as well as the parturient. Because maternal doses are limited by this consideration, pain relief is not sufficiently effective to reverse the adverse maternal effects of labour pain that are described above.

Systemic opioid analgesia

Most studies of fetal/neonatal effects of maternal systemic opioid analgesia have focused on pethidine since it has been around so long; they are summarised in Table 1 and described elsewhere.[26] Detrimental effects may last 72 h or more after delivery and are attributed principally to accumulation of norpethidine.[27] Maximal fetal exposure, and hence neonatal respiratory depression[28,29] and metabolic acidosis[30] are seen if pethidine is given to the mother 3–5 h before delivery, while effects are barely discernible if it is given only within one hour of birth. All neonatal effects are reversed by naloxone, provided a large enough dose, about 0.7 mg/kg intramuscular is given.[31] Although its delayed and prolonged detrimental effects have been known for many years and recently confirmed in a placebo-controlled double-blind trial,[30] some carers persist in believing that pethidine should not be given shortly before birth, but that earlier is OK.

There is little to be gained by the use of partial opioid agonists; butorphanol for example produces more sedation than pethidine. Recently, however, remifentanil has been found to produce more reliable analgesia, and usually better Apgar and neurobehavioural scores than with pethidine.[32–34] Despite these apparent advantages, close monitoring of maternal and neonatal respiration is recommended with remifentanil, but not as yet with pethidine. Can this advice be logical?

Such information as is available for the neonatal effects of other opioids is summarised elsewhere.[25,35]

Table 1 Fetal and neonatal effects of pethidine

Fetal effects	Reduced	muscular activity aortic blood flow oxygen saturation short-term heart-rate variability
Neonatal effects	Depressed	Apgar scores Respiration neurobehavioural scores muscle tone and suckling
	A detrimental effect on breast feeding	

Nitrous oxide

Nitrous oxide in the form of Entonox, a pre-mixed 50–50 mixture with oxygen, is the most popular analgesic for labour in the UK, and is used in many commonwealth countries. As a greenhouse gas, its days may be numbered. It has certain theoretical disadvantages for the fetus:

- In an attempt to obtain maximum analgesia, a parturient's tendency to hyperventilate during contractions is exaggerated, resulting in hypoventilation and consequent desaturation between contractions.
- Prolonged administration of nitrous oxide is also associated with inhibition of the enzyme methionine synthase, a theoretical risk for the fetus.

Nevertheless, it appears harmless to the baby, who can excrete it via the lungs after birth.[36] Various volatile anaesthetics have been added to it from time to time to enhance its effect, but they tend to increase sedation more than analgesia. As it is easily self-administered and more effective than pethidine[37,38] (a long-established fact that is again not universally appreciated) but causes less neonatal depression, its popularity is not totally inappropriate.

Neuraxial analgesia

Neuraxial analgesia produces several oft-quoted maternal complications that have potentially detrimental effects on the fetus, but it also has potentially favourable effects (Table 2). It is therefore essential to assess actual neonatal outcome, rather than to make assumptions based on maternal effects or indeed fetal adverse effects.

Neuraxial analgesia comes in many forms. Initially I will consider the evidence for differences in neonatal outcome between neuraxial analgesia in general and non-neuraxial analgesia, and in a later section, the neonatal effects, if any, of varying neuraxial techniques.

Stress and metabolic changes during labour

Numerous studies in the last century demonstrated that epidural analgesia in labour attenuated or eliminated the rises in stress hormones such as epinephrine,[22,39–41] cortisol,[22,41–44] ACTH,[22] peptide hormones[45,46] and angiotensin II.[47] This pacifying effect of epidural analgesia, together with the reduction in harmful maternal hyperventilation, all help to account for the neonatal acid-base benefits described below.

Table 2 Maternal changes produced by neuraxial analgesia that may affect the baby

Potentially unfavourable effects	Hypotension
	Fever
	Increased need for oxytocin
	Prolonged second stage
	Increased need for instrumental delivery
Potentially favourable effects	Reduced maternal stress and hyperventilation (reversal of adverse effects of labour pain)
	Uterine vasodilatation from sympathetic block
	Fewer episodes of Hb desaturation
	Placental drug transfer is unimportant

Fetal effects

Much has been written about the effects of neuraxial analgesia on cardiotocography, Doppler flow studies, fetal oxygen saturation, etc. although these features are rarely shown to correlate with neonatal outcome in normal labour.

Cardiotocography

Continuous cardiotocography is not a reliable predictor of neonatal welfare and may not be trendy for normal labour, but in the UK the use of epidural analgesia is officially considered to make labour 'abnormal'. Consequently cardiotocography is commonly applied and any abnormality in the fetal heart trace readily detected. Loss of short-term variability, decelerations and the occasional major bradycardia may be noted, although a meta-analysis of randomised trials comparing epidural with systemic analgesia found no significant difference in fetal heart rate abnormalities between the groups.[48] In a double-blind randomised comparison of epidural bupivacaine alone or with fentanyl, Porter found more frequent loss of short-term variability in babies whose mothers received fentanyl.[49] Major bradycardias, however, appear not to be an issue with epidural analgesia, with or without opioids,[50] though they have been reported to occur in 15–28% of cases after *intrathecal* sufentanil.[51,52] Meta-analysis demonstrates a significant increase in the incidence of bradycardia after intrathecal opioids compared with epidural opioids or intrathecal local anaesthetics.[53] The focus of such studies has been whether or not these bradycardias are associated with an increased caesarean section rate (apparently not) but ignoring the obvious and much more important question, *are they associated with any adverse neonatal outcome*? There seems to be no evidence that they are.

Doppler velocimetry

Early studies used radio Xenon to measure intervillous blood flow. These showed no change after epidural analgesia in normal pregnancy, but an improvement in preeclampsia.[54,55] With the advent of Doppler flow studies this technique was abandoned. There have been a number of Doppler flow studies of the uterine and umbilical arteries before and after neuraxial analgesia for labour, though usually without controls. Five teams found no change from baseline in umbilical artery resistance following epidural analgesia,[56–60] one of whom found a reduction in resistance in cases of preeclampsia.[60] One study reported a reduction in umbilical artery resistance after epidural analgesia.[61] Four found that epidurals produced no change in uterine artery resistance in normal labour,[56–59] but one reported a reduction in resistance in preeclampsia,[57] while another group reported an *increase* in uterine artery resistance in normal labour,[62] all patients having received epidural analgesia. In the absence of a control group without neuraxial analgesia, it is impossible to assess the implications for the neonate of any of these changes. Increases in uterine, but not umbilical, artery resistance have also been reported after neuraxial anaesthesia for caesarean section,[63] but again without known neonatal consequences.

Fetal oxygen saturation

There have been several studies of fetal oxygen saturation before and after neuraxial analgesia in labour. The first showed no significant changes in oxygen saturation in 17 fetuses after 27 epidural bolus doses.[64] One compared epidural with paracervical blocks in 20 women; in both groups fetal saturation rose initially, then returned to baseline in the epidural group but remained elevated after paracervical block.[65] Three small case series showed no significant changes in fetal saturation after epidural or combined spinal-epidural analgesia.[66–68] One of these sought but found no correlation between fetal saturation values and neonatal acid-base status.[67] A later case-controlled comparison of 75 women with epidural analgesia and 75 without, found a longer first stage with epidurals, but no significant difference between the two groups in fetal saturations throughout labour, caesarean section rate, cord gas analysis or Apgar scores.[69] Only one group of investigators found a fall in fetal saturation after epidural insertion and top-ups, but not after "infusion boluses".[70]

There is clearly no evidence for a consistent affect of neuraxial analgesia on fetal oxygenation, nor that fetal oxygen saturation itself has any predictive value for neonatal outcome. *Maternal* oxygen saturation is influenced by various types of analgesia, but the minor changes that occur have not been shown to influence neonatal outcome.[71]

Perinatal mortality

Perinatal mortality is too rare to be a useful outcome measure in anything but large studies of at-risk babies. When the use of epidural analgesia was expanding rapidly, a retrospective survey in the Cardiff area[72]

Table 3 Perinatal mortality per thousand births in Cardiff (1976)

	No epidural	Epidural	*P*
Overall	19.2	14.8	NS
Intrapartum	1.3	1.3	NS
First week (early neonatal)	10.3	1.1	0.02
Babies >2.5 kg	3.1	1.2	NS
Babies <2.5 kg	99	0	0.023

Data from David and Rosen (1976).[72]

found an overall perinatal mortality rate of 18.8 per thousand births, a caesarean section rate of 6.9% and an epidural rate of 13.7%. In those days epidural analgesia was used preferentially in high-risk labours, more so than in the present day, so the bias would have been against epidurals. There was no significant difference between antepartum or even intrapartum death rates between epidural and non-epidural babies, but deaths in the first week of life were significantly rarer among epidural babies, which was attributable to a huge difference among low birth weight babies (Table 3). This large apparent improvement in early deaths among small babies *could* be accounted for by a greater use of epidurals in the larger centres with better neonatal care, but equally, these figures provide no evidence that epidurals in labour were putting babies, small or large, at any increased risk. Other early surveys also confirmed a reduced mortality among high-risk infants such as twins and breech deliveries,[73–76] following epidural analgesia.

Albeit not randomised trials, these early studies are worth mentioning, as thereafter mortality became too rare to be a useful index of neonatal outcome.

Apgar score and need for resuscitation

Though many studies of labour analgesia pay little attention to details of neonatal outcome, almost all randomised trials include a record of Apgar score, such that they could be subjected to the first meta-analysis in 1998, comparing neuraxial with systemic opioid analgesia.[77] This clearly showed a reduction in the number of Apgar scores below 7 at both 1 and 5 min and less need for resuscitation among babies whose mothers had neuraxial analgesia. The mothers of control babies had pethidine in seven out of nine studies. A more recent multicentre randomised trial compared patient-controlled epidural analgesia (PCEA) using bupivacaine plus fentanyl with patient-controlled intravenous analgesia (PCIA) using fentanyl.[78] There were no differences in mode of delivery, but more babies in the PCIA group had low 1-min Apgar scores and needed naloxone and resuscitation, despite better maternal analgesia in the PCEA group. These findings were confirmed in further large studies and meta-analyses.[48,79,80] True, they could simply reflect the known adverse effect on the neonate of systemic opioids, and the Apgar score is only applicable to the first few minutes of life, so one needs to look further.

Neonatal acid-base status

With the expanding applications of ion-selective electrodes in the 1970s, the technology was enthusiastically applied to mothers and babies during and after labour. Acid-base status has since become the primary yardstick of fetal welfare during labour.

In 1974, three studies of intrapartum acid-base changes with or without epidural analgesia for labour were published,[10–13,81,82] one of which was randomised.[81] They showed that epidural analgesia reduced maternal hypocarbia and maternal and fetal metabolic acidosis and lactate,[83] while greatly mitigating the fall in fetal pH that otherwise occurs during the second stage of labour. These favourable findings were largely ignored by all but a few anaesthesiologists.

By the end of the century, the caesarean section and backache controversies had prompted a flurry of randomised comparisons of epidural with systemic analgesia, enabling meta-analysis of acid-base balance in over 2000 babies in 12 studies and some hitherto unpublished data.[84] This confirmed that umbilical artery pH and base excess were significantly improved among babies whose mothers had received neuraxial analgesia. Constituent trials had used both old-fashioned epidural analgesia with bupivacaine alone and more modern low-dose combinations. Control mothers had had either no analgesia or pethidine (10 studies), butorphanol (1) or fentanyl (1). A later Canadian multicentre study comparing PCEA bupivacaine plus fentanyl with PCIA fentanyl reported, as well as the benefits to Apgar score and need for resuscitation mentioned above, a trend towards improvement in neonatal pH and base excess in the epidural group.[78]

As any differences between groups could simply reflect an adverse effect of systemic opioids, the Dallas team, who had provided by far the largest number of randomised parturients to the meta-analyses, conducted a case-controlled study comparing umbilical artery acid-base status in 110 matched pairs of women who had received either epidural or *no* analgesia.[85] There was no difference in umbilical artery pH, but both PCO_2 and base excess were significantly higher in the epidural group, suggesting a beneficial effect of epidural analgesia on metabolic acidosis, rather than simply a detrimental effect of systemic opioids.

Neurobehavioural assessment

In the last century, various neurobehavioural tests were developed in an attempt to assess the newborn beyond the first few minutes of life. Various tests have been used to examine the effects of epidural analgesia, with variable results.[86] The simplest and most used by anaesthetists, the neurologic and adaptive capacity score (NACS) was designed to discriminate between drug effects and neonatal asphyxia.[87] Though rather insensitive to small effects,[88] it appears to correlate with breast feeding.[89,90]

Meta-analyses of randomized trials revealed no significant difference in NACS between epidural and systemic opioid analgesia,[77] though minor differences depending on epidural technique have been brought to light (see *Variations in neuraxial drugs*).

Breast feeding

Breast feeding is undoubtedly crucial to neonatal welfare, and therefore should be an important outcome measure. It is, however, affected by many variables,[91–94] such as intention to breastfeed, local tradition and support, initial mother-infant contact, education, social class, mode of delivery and, one would think, length of labour. Hence type of analgesia can play only a minor role. Moreover, this large number of interrelated factors emphasises the need for randomised trials to establish a link between neuraxial analgesia and feeding, yet unrandomised studies continue to be reported.[95–109]

The 17 studies summarised in Table 4 are of various types, but in none was the use of neuraxial analgesia *per se* randomised and blinding was not always attempted. Some failed to distinguish between different types of analgesia or confused systemic with neuraxial routes of administration.[99,106] Outcome measures included breast feeding in hospital and/or at 6–8 weeks or months, milk quantity, LATCH or IBFAT score (see Table 4), bottle-feeding etc. Those purporting to show adverse effects of epidural analgesia received disproportionate publicity.[110]

Seven of the 17 studies showed no adverse effect of epidural compared with no epidural or no analgesia.[89,95–97,100,102,109] Three showed no difference between epidural and systemic analgesia,[98,99,108] but in two studies epidural babies performed better than pethidine babies.[95,109] Three studies found that the epidural group performed worse than no epidural group;[101,103,107] in two studies the apparently detrimental effect of epidural analgesia disappeared on logistic regression,[105,106] another showed a beneficial effect of epidural analgesia on lactation[104] and two showed a dose-related detrimental effect of epidural fentanyl.[90,105] Though unconfirmed by two retrospective reviews,[108,109] such a finding would not be surprising, since opioids, even when given epidurally, must enter the maternal circulation before they are eliminated. Nevertheless, a Canadian study showed that, with good support, a breast-feeding success rate of >95% can be achieved after epidural bupivacaine plus fentanyl, with no discernible dose-related effect.[111] Other studies have demonstrated a dose-related adverse effect of *systemic* opioid analgesia on breast-feeding.[94,112–115]

As Leighton and Halpern point out, ''many hospitals have policies for the care of epidurally-anesthetized parturients that ... minimize early postpartum maternal-infant contact'' and that ''in hospitals with nursing policies that minimize ... separation, epidural analgesia has no effect on lactation success.''[116] It is impossible to infer any adverse effect of neuraxial analgesia *per se* from existing studies. The one implication is that, when prolonged epidural analgesia for labour using a local anaesthetic-opioid combination is extended for emergency caesarean section, it is probably preferable for the baby's sake to avoid further opioid epidurally or systemically.

Variations in neuraxial techniques

There are numerous randomised comparisons of the various techniques and drug regimes, but for neonatal outcome many report only the Apgar score, which is barely sensitive enough to detect such subtle changes as are likely to arise. Differences in neonatal outcome are therefore rarely detected.

Several studies have explored the effect of inducing analgesia early or late in labour.[117–120] Chestnut et al. found that late induction was associated with lower cord pH and higher PCO_2 values and greater need for neonatal naloxone.[117,118] This can be explained by early maternal administration of nalbuphine to the group in whom epidural analgesia was deferred. Others reported that induction of neuraxial analgesia early or late had no effect on Apgar score[119,120] or funic acid-base status.[120]

Neither mode of induction (epidural bolus or a combined spinal-epidural approach) nor maintenance with boluses, infusion or PCEA has been shown to affect neonatal outcome.[121,62]

A randomized comparison of single-shot spinal analgesia using low-dose bupivacaine-sufentanil and paracervical block using bupivacaine alone showed that analgesia was better in the spinal group, but umbilical artery pH was significantly lower.[122] This adverse effect could be laid at the door of intrathecal sufentanil, but equally it is consistent with a significant detrimental effect on funic acid-base balance of spinal compared with general and epidural anaesthesia for caesarean section.[123]

Variations in neuraxial drugs

There is little to choose between bupivacaine, levobupivacaine and ropivacaine from the fetal viewpoint. Lidocaine, which produces more motor block, tachyphylaxis and cumulative toxicity than the newer agents,[124] is unsuitable for prolonged labour analgesia.

Fentanyl is the most widely investigated adjunct to local anaesthetics. In a combined series of 400 labouring women who were randomized to receive equianalgesic infusions of either bupivacaine alone or bupivacaine plus fentanyl double-blind,[125] there were no significant differences in Apgar scores or umbilical artery pH, but NACS failed to improve by 24 h in the fentanyl group. Others have detected this same failure to improve with

Table 4 Breast feeding studies; epidural vs. other or no analgesia

	Type of study	Epidural type (*n*)	Controls (*n*)	Outcome measures	Findings
Rajan 1994[95]	Subset of NBT survey ($n = 1064$)	Various	No epidural	Questionnaire at 6 weeks, breast, bottle or a mixture	Epidurals and Entonox no effect on breast feeding. Abnormal delivery, induction, *short* second stage, general anaesthesia and pethidine reduced it
Halpern 1999[96]	Prospective observational, mixed parity	CSE or epidural bup + suf or fentanyl (113)	No epidural (74) (some had systemic opioids)	Telephone interview: breast feeding success at 6 weeks	72% fully breast feeding at 6–8 weeks. No factors relating to labour analgesia had any significant effect on feeding when leaving hospital or 6 weeks later
Albani 1999[97]	Prospective observational, mixed parity $n = 1920$ vaginal deliveries	*n/k*	No analgesia	Feeding at discharge	Vaginal: epidural 96.5% v. controls 97.8% (NS) caesarean section: neuraxial 95% v. general anaesthesia 85% ($P = 0.002$)
Riordan 2000[98]	Prospective observational, parity not known	Various drugs and doses, usually bup + fent (27)	No mediation (37); i.v. (52); i.v. + epidural (13)	IBFAT, LATCH assessment not properly blinded. Duration of breast feeding at telephone at 6 weeks	LATCH score better with no medication. IBFAT score no med > i.v. = epidural > both. Low IBFAT = shorter feeding but unmedicated did not feed longer than the rest.
Ransjo-Arvidson 2001[99]	Prospective observational, parity not known	Epidural bup *or* pethidine (?systemic) *or* combination (12)	No analgesia (10); mepivacaine pudendal block (6);	Video of infant behaviour immediately after delivery, assessed blindly. Age and duration of first suckling	Unmedicated infants more active
Radzyminski 2003[100]	Observational ($n = 56$)	Ultra low-dose bup + fent	No analgesia	Premature infant breast feeding behaviour scale at birth and at 24 h	No significant difference between groups in breast feeding behaviour
Henderson 2003[101]	Observational nullipara	PCEA bup + fent 5 μg/ml (690)	Support + N_2O + peth (302)	Timing + quality of 1st feed. Duration of feeding or still feeding at 6/12	Still feeding at 6/12: epidural 38%; controls 51%. Factors favouring longer breast feeding: tertiary education > older mothers > non-smoker > no epidural
Baumgarder 2003[102]	Sequential mixed parity	Not stated (115)	No epidural (116)	2 successful feeds in 24 h LATCH score	Success in 24 h: epidural 69.6%; controls 81%; OR 0.53 (NS). Odds of success increased with duration of epidural, to >1
Volmanen 2004[103]	Retrospective, vaginal delivery nullipara	Bup (30) + fent (8)	No epidural (34)	Postal questionnaire Fully breast feeding in 1st 12 weeks	Fully breast-feeding: epidural 33%; controls 71% (usual reason for failure: not enough milk) Factors favouring full breast feeding: younger mothers, no epidural, NOT rooming in, early skin contact, education.

Chang 2005[89]	Prospective cohort; mixed parity	Not stated (52)	No analgesia 63	8–12 h initiation (LATCH) 4/52 continuation + NACS 8-128 h	Breast feeding effectiveness ∝ NACS, no difference between groups Still feeding 4/52: epidural 86%, controls 81% (NS)
Wang 2005[104]	Observational parity *n/k*	Not stated (96)	No epidural 74	Analgesia; mental state; time starting lactation; milk quantity; prolactin	Epidural better analgesia and mental state; quicker lactation; more milk; higher prolactin
Jordan 2005[105]	Retrospective cohort nullipara	Neuraxial (232) [containing opioid 158]	N_2O and/or i.m. pethidine (570)	Feeding on hospital discharge in discharge summary (exclusive or partial breast feeding cf bottle-feeding)	Bottle-feeding on discharge: N_2O only: 32%; i.m. pethidine: 41%; neuraxial local anaesthetic alone: 44%; neuraxial with opioid 53% (NS). Final logistic regression model predictors of bottle-feeding: maternal age, feeding intention, caesarean section and fentanyl (dose-dependent ↑bottle feeding)
Beilin 2005[90]	Randomised double-blindmultiparae who had previously breast-fed	Infusion of bup with low-dose fent (LF, $n = 59$) or high-dose (HF, $n = 57$)	*Epidural* infusion: bup alone (no fent: 0F, $n = 60$)	Day 1: maternal questionnaire, lactation consultant assessment, NACS. Telephone enquiry 6 weeks	Maternal assessment at 24 h correlated with NACS and subsequent performance, lactation consultant's did neither. Not breast feeding at 6 weeks:0F: 2%; LF: 6%; HF: 19% ($P = 0.002$)
Torvaldsen 2006[106]	Prospective cohort; singleton mixed parity. *No selection of those intending to breast-feed*	PCEA bup + fent 3.3 μg/mL All had i.m. pethidine (416)	Non-pharmacologic/ N_2O/pethidine (762)	Questionnaires on discharge and 8, 16 and 24 weeks: fully, partial or not breast-feeding. Hazard ratio of stopping feeding in 24 weeks	Only less educated did not breast feed at all. Predictors of partial breast feeding 1st week: young mothers > less education > delivery type & analgesia: general anaesthesia > epidural > N_2O > none > pethidine! After adjusting for delivery type and parity, epidural effect NS. Breast feeding at 24 weeks: no analgesia 72%; no epidural 64%; epidural: 52%. Predictors of stopping in 24 weeks: young > education > analgesia
Wiklund 2009[107]	Retrospective all epidurals; controls matched for parity, age and gestation	Usually bup + sufentanil bolus or infusion ± paracervical and/or pudendal block (351)	Nothing or paracervical and/or pudendal blockNo opioid (351)	Breast feeding in 1st 4 h; artificial milk given; breast feeding at discharge	Babies in the epidural group were less likely to breast feed in the first 4 h (OR 3.79), more likely to be given artificial supplement (OR 2.19) and less likely to be breast feeding at discharge (OR 1.79)

(*continued on next page*)

Table 4 (*continued*)

	Type of study	Epidural type (*n*)	Controls (*n*)	Outcome measures	Findings
Jordan 2009[108]	Retrospective review of 18165 Cardiff births over 10 years *No selection of those intending to breast-feed*	Not stated	Not stated	Regression analysis factors in breast feeding at 48 h, in 44641 women, mixed parity	Strongest association with breast feeding at 48 h: social class 1 > primparity > oxytocic third stage > analgesia (epidural vs i.m. opioid NS). Length of labour not included in regression analysis
Wilson 2010[109]	COMET plus no epidural controls matched for parity, del type and ethnicity	CSE + low-dose bup + fent bolus (351) *or* LDI: low-dose bup + fent infusion (350) *or* high-dose bup boluses (353)	Pethidine (151) or no analgesia (200)	Interviewed 24–48 h? initiated breast feeding. Postal questionnaire 12 months: duration of breast feeding	Number initiating breast feeding: all epidural groups and no analgesia group NS; pethidine group lower initiation rates ($P < 0.001$). Dose of fentanyl: not predictive. Duration NS

NBT: national birthday trust; IBFAT: infant breast feeding assessment tool; LATCH: L denotes how well the infant latches onto the breast; A: audible swallowing; T: nipple type; C: maternal comfort; H: amount of help the mother needs. bup: bupivacaine; suf: sufentanil; fent: fentanyl; peth: pethidine; PCEA: patient-controlled epidural analgesia; NACS: neurologic and adaptive capacity score; CSE: combined spinal-epidural; LDI: low-dose infusion; NS: not significant; OR: odds ratio; COMET: comparative obstetric mobile epidural trail.

fentanyl,[126] which supports the finding that larger doses of fentanyl may be associated with slightly impaired breast feeding.[90,105] In a double-blind comparison of 50-, 75- or 100-μg loading doses of epidural fentanyl, followed by infusion of fentanyl plus bupivacaine, sadly only Apgar scores were recorded and did not differ between groups.[127] While epidural fentanyl may increase the number of episodes of maternal desaturation, such episodes have not been found to correlate with funic pH or NACS.[71] In a double-blind comparison of epidural bupivacaine infused alone or with fentanyl, the addition of moderate doses of fentanyl to epidural bupivacaine had a negligible effect on neonatal respiration.[128]

It is perhaps not surprising if fentanyl is associated with delayed neonatal recovery, since it is bound principally to albumin, hence becomes unbound during the first day of life (see *Placental drug transfer*).

Russell et al. in a double-blind comparison of fentanyl and sufentanil by infusion, found no difference in Apgar scores, cord pH or NACS,[129] while Loftus et al., who gave sufentanil in relatively larger doses, reported less placental transfer, a significantly higher PCO_2 but better 24-h NACS scores with sufentanil.[126] *Intrathecal* sufentanil, on the other hand, is associated with a significantly disturbed fetal heart trace and uterine hyperactivity,[53,130] though again a difference between sufentanil and fentanyl is not established.[131]

Any neonatal effects of epidural fentanyl are mild and outweighed by the outstanding maternal benefit and increased safety of the low-dose combination. The same cannot be said of neuraxial *clonidine* and *epinephrine*, whose benefits are marginal but whose detrimental neonatal effects are more consistent. The addition of clonidine to epidural ropivacaine was associated with reduced Apgar score and NACS,[132] while a 30-μg intrathecal dose exacerbated fetal heart rate abnormalities and neonatal acidosis.[133] The addition of epinephrine 1:800 000 to epidural solutions not only increases motor block, making it unsuitable during labour, it has also been associated with reduced Apgar scores,[134] though this is not a consistent finding.[135]

In future any randomised trials involving variations in neuraxial techniques, drugs or doses should include full neonatal assessment, including Apgar scores, acid-base balance, neurobehavioural scores and breastfeeding, preferably studied blindly. Meanwhile, such evidence as there is, particularly that arising from rock-solid acid-base balance studies, suggests that the newborn is *not* destined to suffer as a result of maternal neuraxial analgesia in labour.

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