**ESTIMATION OF INFANT DOSE AND EXPOSURE TO
PETHIDINE AND NORPETHIDINE VIA BREASTMILK
FOLLOWING PATIENT-CONTROLLED EPIDURAL PETHIDINE
FOR ANALGESIA POST CAESAREAN DELIVERY**

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ABSTRACT

Introduction: There is no information about the distribution of pethidine into breastmilk and/or of exposure of the breastfed infant after patient controlled epidural analgesia (PCEA) with pethidine after caesarean delivery.

Methods: We conducted an observational study among 20 women receiving pethidine PCEA after elective caesarean delivery. The mean (95% confidence interval) dose administered was 670 (346-818) mg over 41(35-46) hours. Maternal plasma and milk and neonatal plasma were collected around the time of PCEA cessation (approximately 48 hours from time of operation) and six hours later. Drug concentrations measured by liquid chromatography-tandem mass spectrometry. Absolute infant dose (AID) was calculated from the milk concentration of pethidine and norpethidine and the calculated daily milk volume. Relative infant dose (RID) was derived from the AID divided by the weight-adjusted maternal dose of pethidine used until cessation of PCEA. Infant doses via milk and infant exposure were calculated. Infant neurobehaviour was assessed using the Neonatal and Adaptive Capacity Score (NACS).

Results: At the first and second sampling times, mean AIDs for pethidine were 20(14-27) $\mu\text{g/kg/d}$ and 10(7-13) $\mu\text{g/kg/d}$, while mean RIDs were 0.7 (0.1-1.4) % and 0.3(0.1-0.5) % respectively. For norpethidine (expressed as pethidine equivalents), mean AIDs were 21(16-26) $\mu\text{g/kg/d}$ and 22(12-32) $\mu\text{g/kg/d}$, while mean RIDs were 0.7 (0.3-1) % and 0.6(0.2-1) %, respectively. Mean pethidine and norpethidine concentrations in neonatal plasma were 3(zero-6.1) $\mu\text{g/L}$ and 0.6(0.2-1) $\mu\text{g/L}$ respectively. Compared to a time-matched maternal plasma sample, the infant's exposure to maternal pethidine was 1.4 (0.2-2.8) % for pethidine and 0.4(0.2-0.6%) for norpethidine. Mean NACS scores of 33.5 (30-36) were normal.

Conclusions: The combined AID of pethidine and norpethidine received via milk was 1.8% of the usual therapeutic dose for neonates and the combined RID was well below the 10% recommended safety level. There was no evidence of neurobehavioural deficit. Breast-fed infants are at a low risk of drug exposure when mothers are self-administering epidural pethidine after caesarean delivery.

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My role was pivotal to the design, hypothesis and implementation of this project. I undertook the original reading, submitted the proposed study for ethics approval at KEMH for women and organised the team of collaborators at UWA and Path West to consult with the clinical research group in the Department of Anaesthesia and Pain Medicine. My role involved designing the information sheet for patients, drafting the data collection sheet and reviews all supportive documentation prior to commencing recruiting participants into the trial. I piloted five patients initially to examine the flow of sample collection and data entry, and then decided to continue according to the methodology. The research midwives at KEMH gathered the rest of the data and stored all the milk and plasma samples. The two research midwives were well trained in doing so and also conducted all NACS testing and recording. I followed this process on a weekly basis and reviewed data entry accordingly. All samples were analysed at Path West Laboratories in Perth, Western Australia. Pharmacological data were examined by myself and co-analysed with E/Professor Ken Ilett. The timing of sampling in relation to time of birth for calculation of milk volume was suggested by the latter based on published work as outlined in Chapter Two of this thesis. Data verification and tabulation was conducted by me, assisted by E/Professor Ilett. The appendices on pharmacological analysis were written by the latter and Mr. Sean O'Halloran of Path West.

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Publications, Abstracts and Presentations Arising from this Thesis

Publication:

Y. Al-Tamimi, K.F. Ilett, M.J. Paech, S.J. O'Halloran, PE Hartmann. Estimation of infant dose and exposure to pethidine and norpethidine via breastmilk following patient-controlled epidural pethidine for analgesia post caesarean delivery. International Journal of Obstetric Anaesthesia (2011) 20, 128-134.

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Estimation of infant dose and exposure to pethidine and norpethidine via breast milk following patient-controlled epidural pethidine for analgesia post caesarean delivery.

Abbreviations

ABS Australian bureau of statistics

AID Absolute infant dose

ANZCA Australia and New Zealand College of Anaesthetists

ARC Australian Research Council

ASA American Society of Anesthesiologists

AUC area under the curve

BMI body mass index

CBM computerized breast measurement

CDC [Centers for Disease Control](#)

CGRP Calcitonin G-related peptide

CI confidence interval

cm centimeters

Cmax Concentration maximum

CNS central nervous system

COX Cyclo-oxygenase

CS Caesarean section

CSE combined spinal epidural

CSF Cerebro-spinal fluid

CV coefficient of variance

FHR Foetal heart rate

g gram(s)

Glu glutamate

H hour

HR Hazard ratio

IBFAT infant breast feeding assessment tool

IM intramuscular

IQR interquartile range

IUD intrauterine death

IV intravenous

IVC Inferior vena cava

Kg kilogram(s)

LATCH-R latch, audible noise, type of nipple, comfort, help needed, responsiveness

LC liquid chromatography

m meter

MAOI Mono amine oxidase inhibitor

MBAT mother-baby assessment tool

mcg micrograms

MEAC minimum effective analgesic concentration

mg milligrams

ml milliliters

mm millimeters

M/P Milk/Plasma ratio

MPTP Methyl phenyl tetra pyridine

MS mass spectrometry

NACS neonatal and adaptive capacity score

NBAS Neonatal Behavioural assessment scale

NHMRC National Health and Medical Research Council

NRS numerical rating scale

NSAID non steroidal anti-inflammatory drug

OR Odds ratio

PCA patient controlled analgesia

PCIA patient controlled intravenous analgesia

PCEA patient controlled epidural analgesia

P probability

PG Prostaglandin

PO per oris

PONV post-operative nausea and vomiting

RR Risk ratio

RID Relative infant dose

SC Subcutaneous

SD standard deviation

SIBB Suboptimal infant breastfeeding behaviour

Sp Substance p

SR sustained release

T_{1/2} half time

TDLU Terminal duct lobular unit

UK United Kingdom

USA United States of America

UWA University of Western Australia

V volume

VAS visual analogue scale

vs. versus

WHO World health organisation

Statement of Candidate Contribution

I hereby, declare that this thesis is based on research conceived, designed and conducted by myself and colleagues at King Edward Memorial Hospital and UWA. Some sections of this thesis have parts which were co-authored with E/Professor Ken Ilett. Professor Ilett has helped me with the supply of Sigma Plot software which was necessary for the statistical and graphical part of section two of the thesis (analytical pharmacokinetics). He and my supervisor, who has been involved in the project since inception, are also co-authors of the journal article that I published as the main author in the International Journal of Obstetric Anaesthesia in April 2011.

I planned the project myself, gathered the collaborative support, applied for ethics approval and gained the grant support. I have written more than 95% of the thesis; my supervisor has coached the process of writing and edited the document as it progressed towards completion. Emeritus Professor Ken Ilett had supplied the logistic support through his team at Path West laboratories at Queen Elizabeth II Medical Centre, to conduct the drug assays and assist in interpreting the results. I will attach this declaration with my thesis document upon submission.

Student Signature

Coordinating Supervisor Signature

Chapter One: Literature Review:

1.1 Introduction:

Over the last two decades the number of caesarean deliveries being performed has increased dramatically. It is estimated that between 10-36% of Australian pregnant women have undergone caesarean delivery in the last decade. This incidence appears to be on the rise (National statistics on Caesarean section rates 2005).

Breastfeeding is recognised as being one of the ‘most natural and best forms of preventive medicine’ and is promoted internationally as the preferred method of feeding for infants up to the age of six months. Breast feeding is a complex physiological function which may be affected by a variety of demographic, social, biological, psychological and pharmacological factors. The initiation and maintenance of successful breastfeeding is not only vital for early neonatal-maternal bonding but also confers important and potentially long-term health benefits to the infant.

Pethidine analgesic properties were discovered in Germany in 1939 and clinical use followed almost immediately. It is widely used in birth suites in Australasia and the United Kingdom, mainly via the parenteral (intramuscular) route. The potentially harmful effects of parenteral pethidine on neonates were demonstrated more than two decades ago. However, it is still uncertain whether epidural opioids (namely fentanyl, morphine and pethidine) administered to women during labour and after caesarean birth have adverse effects on the newborn baby. The likely effects on breastfeeding, if these exist, have been poorly studied. To date, no national or international guidelines exist to guide clinicians or patients as to the safety of epidurally-administered opioids in the breastfeeding mother and her baby.

The use of neuraxial techniques (spinal and epidural anaesthesia and analgesia) for both intraoperative anaesthesia and postoperative analgesia is the most popular approach currently because evidence suggests that it is safer, at least for mothers, than general anaesthesia. The choice of postoperative epidural analgesia rather than other analgesic methods depends on the anaesthetist’s skills and preferences, the hospital services (acute pain services and midwifery or nursing accreditation to manage and monitor epidural analgesia) and local and hospital guidelines. In Australia and New Zealand, epidural pethidine and morphine are the most popular opioids for women who have

caesarean birth and who consent to an epidural analgesic method. Epidural pethidine may be administered by the nursing staff, when requested by the patient, in a 25-50mg bolus at 1-2 hourly intervals, or by means of a Patient-Controlled Epidural Analgesia (PCEA) device. At the study institution, the available device allows the patient to self-administer 20 mg of pethidine at 15 minute lockout intervals. Subarachnoid opioids like fentanyl, sufentanil and morphine are also widely used locally and abroad and intrathecal morphine remains an attractive choice to achieve prolonged postoperative analgesia after CS. Intrathecal techniques are popular in Australia and North America.

This literature review examines pethidine administered epidurally after caesarean birth and the initiation and quality of breast feeding.

In the first section the general pharmacology of pethidine is reviewed, followed by parenteral opioid use for labour and post-caesarean analgesia. A detailed account of the pharmacology of epidural pethidine follows, with a focus on mode of action, methods of epidural drug administration and the effects of various neuraxial factors on drug kinetics.

In the second section the physiology of lactation is discussed, with emphasis on the stages of lactogenesis and possible factors influencing the initiation and continuation of breastfeeding. The effects of the mode of delivery on breastfeeding are further considered in detail.

The next section reviews the effects of epidural analgesia on breastfeeding success and duration, with a detailed analysis of the studies which showed an adverse effect versus those showing no adverse effect.

The pharmacological aspects of drug excretion in breast milk are then described with clear demonstration of the interplay of neonatal, maternal and drug factors.

The final section of this review focuses on aspects of measurement. This starts with quantification of drug exposure among breast-fed infants and the methods used to derive infant dose exposure. The methods used to assess the adequacy of breastfeeding, including clinical scores and the latest advances in ultrasound examination, follows.

This review ultimately leads to discussion of pethidine in breast milk and its potential neonatal effects.

1.2 Historic and Basic Pharmacology of Pethidine

The analgesic properties of pethidine were discovered by Eisleb and Schaumann in 1939 when they were investigating the potential spasmolytic properties of compounds with similar structure to atropine (Eisleb V et al., 1939). One year later it was used for labour analgesia in Germany by Benthin (Benthin et al. 1940). Known as meperidine in North America, pethidine was one of the first opioids to be injected epidurally in humans (Ngan Kee 1998).

Pethidine (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate) is a synthetic phenylpiperidine opioid agonist with lipid solubility that is intermediate between morphine and most of the other opioids in clinical use (alfentanil, fentanyl and sufentanil). It is a weak base with pka of 8.5, nearly similar to that of fentanyl.

Figure-1 Chemical Structure of Pethidine

(From Ngan Kee, 1998)

Table-1 physicochemical properties of commonly use opioids

Opioid	Lipid Solubility*	pka	Protein Binding (%)
Morphine	1.4	7.9	35
Pethidine	39	8.5	70
Diamorphine	280	7.8	40
Fentanyl	816	8.4	84
Sufentanil	1727	8.0	93

*Data from Camu F, Vanlersberghe C. Pharmacology of systemic analgesics. Best Pract Res Clin Anaesthesiol 2002; 16:475-88; and McLeod GA, Munishankar B, Columb MO. Is the clinical efficacy of epidural diamorphine concentration-dependent when used as analgesia for labour? Br J Anaesth 2005; 94:229-33. * Octanol-water partition coefficient.*

Pethidine is a moderately lipophilic opioid, making it attractive to use via the epidural route, where it shows a quick onset of analgesic effect and a negligible risk of respiratory depression. It is a mu-opioid receptor agonist and has potent spinal and supraspinal analgesic effects (Ngan Kee, 1998). The elimination half-life ($t_{1/2}$) of pethidine is 3-6 hours (h). It is metabolised in the liver to norpethidine, a pharmacologically active drug that is excreted by the kidneys with a prolonged elimination $t_{1/2}$ (15-33 h). These elimination half lives are twice as long in the neonate (Caldwell J et al., 1978). The central nervous system excitatory effects of these drugs (agitation, tremulousness, hallucinations and convulsions), in particular norpethidine, which has twice the convulsive potency of pethidine, may result in neurotoxicity after intravenous (IV) administration of large doses, prolonged administration of moderate doses, or the presence of renal dysfunction. Systemic levels of pethidine fall steadily after cessation of administration in patients with normal renal function, but norpethidine levels may continue to rise.

The neurotoxicity of the principal pethidine metabolite is a unique feature of pethidine compared to other opioids. Pethidine metabolites are further conjugated with glucuronic acid and excreted into the urine. These toxic effects can not be blocked by the mu-opioid antagonist (naloxone) as they are not completely mediated via mu-opioid receptors (Caldwell J et al. 1978).

Adverse Effects and Drug Interactions:

In addition to the adverse effects common to all opioids, such as constipation, dry mouth, lightheadedness, itchiness, muscular twitches and nausea, the repeated administration of pethidine can lead to neurotoxicity. As well as the parent drug pethidine and its metabolite norpethidine, a neurotoxic impurity may be present in pethidine. It is *N*-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine (MPTP), a synthetic substance derived from the hydrolytic degradation of an ester group. MPTP is a very toxic compound, implicated as the cause of severe and irreversible Parkinson's-like symptoms. This impurity causes the destruction of nigrostriatal dopamine neurones, leading to symptoms that closely resemble those present in human idiopathic

Parkinson's disease. Despite extensive purification of pethidine, the drug may still contain traces of MPTP (Quaglia MG et al. 2003). There is no information available regarding a formulation of pethidine that does not contain MPTP byproduct, which arguably raises concerns about the safety of pethidine in general.

Central nervous system effects (confusion, anxiety, nervousness, hallucinations, twitching, and seizure) have been documented in approximately 14% of patients receiving IV pethidine (Seifert CF& Kennedy S 2004).

Skin reactions and histamine release from mast cells have been reported after pethidine IV patient-controlled analgesia (PCA) (van Voorthuizen T et al., 2004). Serious tachydysrhythmias after acute myocardial infarction (Kredo T& Onia R. 2005) and delirium in elderly patients have also been reported (Adunsky A et al. 2002)

Pethidine has serious drug interactions that can be dangerous, especially with monoamine oxidase inhibitors (MAOIs) (such as furazolidone, isocarboxazid, linezolid, moclobemide, phenelzine, procarbazine, selegiline, and tranylcypromine), naltrexone, ritonavir, and sibutramine (Bowdle TA 1998). Patients may suffer agitation, delirium, headache, convulsions, and/or hyperthermia. These symptoms are thought to be caused by an increase in cerebral serotonin concentrations (Sporer KA 1995; Bonnet U 1993). Pethidine can also interact pharmacodynamically with a number of other medications, including muscle relaxants, some antidepressants, benzodiazepines, and alcohol.

Several fatal reactions have been reported after co-administration of pethidine with an MAOI. Pethidine should not be used within a 14-day period of stopping a MAOI (Kredo T& Onia R. 2005). Furthermore, relatively commonly used drugs (such as theophylline, tricyclic antidepressants, and the fluoroquinolones) can potentiate the potential for pethidine to cause seizures (Thompson DR 2001).

Pethidine is relatively contraindicated when a patient is suffering from liver or kidney disease, has a history of seizures or epilepsy, has an enlarged prostate or urinary retention or suffers from hyperthyroidism, asthma or Addison's disease (Quaglia MG, Farina A, Donati E, et al.2003; Van Voorthuizen T et al. 2004; Shipton EA 2006).

1.3 Parenteral Opioid Analgesia in Labour

Despite the wide availability of neuraxial techniques, parenteral opioids are still popular in many maternity units and hospitals. In the United States a survey identified between 34% and 42% of women in labour received parenteral drugs for analgesia in 2001, in contrast to 50% in 1981 (Bucklin et al. 2005). The latest Australian data shows 25% of women using parenteral opioids in labour (Australian Mothers and Babies 2007, Australian Institute of Health and Welfare). Although the use of neuraxial techniques is on the rise, this still means that a large proportion of women still use parenteral opioids during the course of labour, with or without a neuraxial technique (spinal, epidural or combine spinal-epidural CSE) (United kingdom National Health Services 2005-2006).

The use of systemic analgesia remains common practice in many institutions in many parts of the world, for several reasons. Many women deliver in environments where safe neuraxial labour analgesia is not available. In some countries, including Australia, the administration of systemic opioid by midwives, without medical prescription, is permitted. Some women decline neuraxial analgesia or choose to receive systemic analgesia in the early stages of labour. Finally, some women may have a medical condition that contraindicates neuraxial procedures (e.g. coagulopathy) or contributes to a technically difficult or impossible procedure (e.g. lumbar spine surgery) (Fernando R& Jones T 2007).

Although systemic opioids have long been used for labour analgesia, little scientific evidence suggests that one drug is significantly better than another for this purpose; most often the selection of an opioid is based on institutional tradition and/or personal preference. These drugs commonly cause nausea, vomiting, delayed gastric and bowel emptying, drowsiness, dysphoria, and hypoventilation. There is also a risk of placental transfer to the fetus, with potential for neonatal depression and lower Apgar scores at birth (Fernando R& Jones T 2007).

The intravenous (IV) route is preferred over the subcutaneous (SC) or intramuscular (IM) routes of administration because of (1) faster onset of analgesia (2) less variability in the peak plasma concentration of drug; and (3) the ability to titrate dose to effect (Fernando, Jones 2007).

1.3.1 Parenteral Pethidine for Labour Analgesia

Pethidine is the most commonly used opioid for labour analgesia. Eighty four percent of birth units in the UK prescribe pethidine for labour analgesia (Tucky et al. 2008). A 100 mg IM dose may be given once or twice in the course of labour, but not close to delivering the baby. Familiarity, ease of administration, low cost, and lack of evidence that alternative opioids show any benefits over pethidine have encouraged its widespread use.

Saravanakumar et al in their survey of the UK practice of labour analgesia have shown that when neuraxial analgesia is contraindicated, IM opioids were prescribed in almost all units surveyed (alone or in combination with other analgesic agents) (Saravanakumar et al. 2007).

Figure-2 various methods of analgesia when epidural analgesia is contraindicated (UK Survey)

Labour analgesia when regional techniques are contraindicated or technically impossible. TENS: Transcutaneous Electrical Nerve Stimulation; IM: Intramuscular; SC: Subcutaneous; PCIA: Patient Controlled Intravenous Analgesia. (From Saravanakumar et al. 2007)

The first double-blinded trial (with 224 women enrolled) compared IM pethidine with IM placebo in 1964. Data were limited to maternal and caregiver's satisfaction with

labour pain relief. Significantly more women were dissatisfied with pain relief in the placebo group when assessed during labour (71% vs. 83%, $p = 0.04$) and after birth (25% vs. 54%, $p = 0.00004$). Significantly more caregivers were dissatisfied with placebo (De Kornfeld TJ et al. 1964). Recently, there have been significant doubts as to the efficacy of pethidine. Some studies have demonstrated that less than 20% of women obtain satisfactory pain relief (Ranta et al. 1994). A Swedish study compared nulliparous women in active labour receiving IV pethidine or morphine in repeated doses. The authors concluded that systemic opioids are not effective analgesics for labour pain (Olofsson et al. 1996).

Fairlie et al conducted a randomised trial to investigate the efficacy of IM pethidine and IM diamorphine in the U.K (Fairlie et al. 1999). Both nulliparous and multiparous women were recruited into the trial and women who delivered within 60 minutes of having the trial drug were excluded from analysis. There was no statistically significant difference between the groups in visual analogue score (VAS) for pain 60 minutes after trial entry, but there was an overall trend for more women who received pethidine to report a moderate or severe pain intensity, compared with those who received diamorphine, 60 minutes after receiving the trial drugs. This reached statistical significance for multiparous women (RR 0.84, 95% CI 0.72 to 0.98; $P = 0.02$), but not for nulliparous and multiparous groups combined (RR 0.92, 95% CI 0.79 to 1.08; $P = 0.43$). Almost 50% of the women in the trial reported the trial drug provided poor pain relief, irrespective of whether it was diamorphine or pethidine. The incidence of a request for 'second line analgesia-either epidural analgesia or a second dose of opioid' was not different between the two groups. More nulliparous women requested second line analgesia than multiparous women, reflecting the shorter length of labour in the latter group. The authors reported a significantly higher incidence of low 1- minute Apgar scores in the IM pethidine group and suggested that IM diamorphine may still have a role in labour analgesia (Fairlie et al. 1999).

One randomised, placebo-controlled, double-blinded study of IM pethidine (100 mg) for labour analgesia identified some benefit. The study was terminated prematurely when interim analysis revealed that pethidine produced a significantly greater reduction in visual analog scale (VAS) pain scores than placebo. The analgesic effect was modest, however, with a median change in VAS pain score of 11 mm (95% CI of 2-26 mm,

using a 100-mm scale) at 30 minutes (Tsui MH et al. 2004). The requirement for and timing of subsequent analgesia is shown in the survival curve in figure 3. The mean time to first subsequent request for analgesia was greater in the pethidine group (232 minutes, 95% CI 135-329 minutes) compared with the control group (75 minutes, 95% CI 54-95 minutes). Eight (32%) of the pethidine group needed no further analgesia compared with one woman (4%) in the control group ($P=0.011$) (Tsui MH et al. 2004).

Figure-3 Kaplan-Meier Curve for the placebo and intramuscular pethidine groups

Kaplan–Meier survival plot showing the need for further analgesia before delivery. Survival time was defined as the time from initial injection to first subsequent request for analgesia. Cases were considered censored (represented by circles) if they delivered without the need for further analgesia. The pethidine group is represented by the full line; the control group is represented by the dotted line. (From Tsui MH et al. 2004)

Tsui MH et al study showed that satisfaction scores at 30 minutes were greater in the pethidine group (median 2, interquartile range 2–3) compared with the control group (median 1, interquartile range 1–2, $P < 0.001$).

The Tsui et al study has been criticised for being biased in its selection of patients (it excluded those who had decided to have epidural analgesia). Moreover, of all the women who matched the study inclusion criteria, only a quarter was subsequently randomised. More than half of the women initially approached would not agree to

randomisation and a further half of the women who were agreeable did not enter the study for various reasons. Thus, their participants were highly selected and it can be argued that their pain threshold and response to therapy may not necessarily have been representative of the general population.

When IM pethidine is compared to various other opioids, maternal pain relief appears almost identical among the various groups, whether assessed as maternal satisfaction with pain relief, VAS pain scores, or use of other pain relief or epidural analgesia (Bricker, Lavender 2002).

Nel et al compared different doses (40 and 80 mg) of pethidine in the first stage of labour. The larger dose conferred better analgesia in terms of lower VAS pain scores and need for further analgesia (Nel et al. 1981). Nelson and Eisenach conducted a study to compare pethidine, butorphanol and their combination during labour. The authors concluded that IV butorphanol, 1 mg, and meperidine, 50 mg, reduce pain intensity and pain affective magnitude by a statistically significant amount 15 minutes after injection, in women with moderate to severe labour pain. The authors also confirmed that it is ethically appropriate to administer systemic opioids to women requesting analgesia for labour pain. However; a minority of women receiving these drugs achieved pain intensity reductions large enough to meet criteria for meaningful pain relief. This suggests that these drugs, at these doses, are not ideal for treatment of pain in this setting, and that other approaches, including new drugs, are necessary for reliable pain relief (Nelson & Eisenach 2005).

Intramuscular pethidine (50 and 100 mg) was compared to 10 mg of IM ketorolac and the authors noted significantly better analgesia in the pethidine group, although lower Apgar scores at one minutes were seen in the pethidine group. The effect on Apgar score was no longer present 5 minutes after birth (Walker et al. 1992)

When comparing IV pethidine in labour to other opioids, a systematic review found no difference in analgesia, with the exception of better pain relief from IV fentanyl compared to IV pethidine. Maternal, neonatal outcomes and adverse events were comparable (Bricker& Lavender 2002). There were also no differences in outcomes between intermittent IV boluses of pethidine and pethidine PCA, due to insufficient data.

Maternal, fetal, and neonatal side effects are ongoing concerns with pethidine administration. Maternal nausea, vomiting, and sedation are common. Fetal and neonatal effects result from the pharmacokinetic properties of pethidine. Pethidine readily crosses the placenta and equilibrates between the maternal and fetal compartments within 6 minutes (Shnider et al. 1966). Decreased FHR variability occurs 25-40 minutes after IM administration and resolves within an hour (Kuhnert et al. 1979). Neonatal half life is prolonged, at 18-23 hours. Norpethidine is the active metabolite of pethidine and has a half life of 60 hours in the neonate (Caldwell et al. 1978).

Neonatal complications after IM pethidine relate to the total dose of pethidine and the dose-delivery interval. Maximal fetal uptake of pethidine occurs 2 to 3 hours after maternal administration and studies have shown that infants born within this interval have an increased risk of respiratory depression (Shnider & Moya 1964; Kuhnert et al. 1979). Norpethidine accumulates after multiple doses or after a prolonged dose-delivery interval (Belfrage et al. 1981) and may be associated with altered neonatal neurobehavioural state, including reductions in the duration of wakefulness and attentiveness, and impaired breastfeeding (Belfrage et al. 1981; Hodgkinson et al. 1978; Belsy et al. 1981; Kuhnert et al. 1985 and Nissen et al. 1997).

The effect of pethidine on the progress of labour is contentious. Some obstetricians argue that it may prolong the latent phase of labour, but others administer pethidine to shorten the length of the first stage of labour in cases of dystocia. Sosa et al., concluded that pethidine does not benefit labour progress in women with dystocia and should not be used for this indication because of the greater risk of adverse neonatal outcome compared with placebo (Sosa et al., 2004).

1.3.2 Pethidine Patient-Controlled Analgesia in Labour:

Patient-controlled analgesia (PCA) is widely used in the management of postoperative pain. Although continuous IV infusion of opioids has been used for at least four decades, the growing popularity of PCA for postoperative analgesia has prompted the use of this technique for labour analgesia. A 2007 survey of United Kingdom practice

showed that 49% of labour and delivery units offered PCA for labour analgesia (Saravanakumar et al. 2007).

Figure-4 PCA use in labour (UK data)

Number of units using opioid patient-controlled intravenous analgesia (PCIA) for labour pain. IUDs: Intra-uterine deaths. (From Saravanakumar et al. 2007)

Purported advantages of PCA are (1) superior pain relief with lower doses of drug; (2) less risk of maternal respiratory depression (compared with bolus IV administration); (3) less placental transfer of drug; (4) less need for antiemetic drugs and (5) higher patient satisfaction (McIntosh DG, Rayburn WF, 1991). More frequent administration of small doses of drug should achieve a more stable plasma drug concentration and a more consistent analgesic effect (McIntosh DG, Rayburn WF, 1991).

PCA for labour is not without limitations. Despite frequent administration, small doses of opioid may not always be effective for the fluctuating intensity of labour pain, especially in the late first stage or second stage of labour (McIntosh DG, Rayburn WF, 1991). Moreover, the risk to the fetus and neonate remains unclear; studies have used variable methods of neonatal assessment. Variable doses and lockout intervals have been used, including PCA with and without a continuous infusion. Pethidine, nalbuphine, fentanyl, and more recently, remifentanyl have been the opioids most commonly used for PCA. The most appropriate drug, dose, and dosing schedule has not, however, been defined.

PCA offers an attractive alternative for labour analgesia in hospitals in which neuraxial anesthesia is unavailable, or either contraindicated or unsuccessful. The woman can tailor the administration of analgesic drug to her individual needs. Although PCA may result in higher patient satisfaction than other methods of systemic opioid

administration, most studies have not demonstrated reduced drug use or improved analgesia with PCA compared with IV opioid administration by the obstetric nurse (Fernando R, Jones T., 2009). Isenor and Penny-McGillivray compared intermittent IM boluses of pethidine (50 to 100 mg every 2 hours) and pethidine PCA (background infusion 60 mg/hr; PCA bolus 25 mg to a maximum dose of 200 mg). Women in the PCA group received more pethidine and had lower pain scores than women in the control group. Even when controlling for dose, pain scores were lower in the PCA group. There was no difference in maternal side effects, FHR tracings, or Apgar scores between treatment groups in this small study (Isenor L& Penny-McGillivray T, 1993)

The UK data on use of PCA in labour demonstrated that remifentanyl, morphine and other opioids are more popular in birth suites than pethidine PCA (Saravanakumar et al. 2007). No published Australian data are available. Personal communication with birth suites in Perth, Western Australia revealed that fentanyl and remifentanyl were the drugs of choice.

Pethidine PCA has disadvantages when compared with PCA using shorter-acting opioids. Volikas and Male compared pethidine PCA (bolus 10 mg, lockout interval 5 min) with remifentanyl PCA (bolus 0.5 µg/ kg, lockout interval 1-2 min). The study was terminated after enrolment of 17 subjects because of concern about poor Apgar scores in the pethidine group (median 1- and 5-minute scores of 5.5 and 7.5, respectively) (Volikas I& Male D, 2001).

Figure- 5 VAS pain scores for pethidine and remifentanyl PCA in labour

*Mean (standard deviation) hourly visual analogue scale (VAS) pain scores for the remifentanyl and pethidine groups. * P = 0.01 (From Volikas, Male. 2001)*

Other researchers also compared pethidine PCA (bolus of 15 mg, lockout interval 10 min) with remifentanyl PCA (bolus of 40 µg, lockout interval 2 min). VAS for pain were similar in the two groups, although satisfaction scores during the study were higher in the remifentanyl group at 60 min (median (interquartile range [range]) 8.0 (7.5–9.0 [4.0–10.0])) than those in the pethidine group (6.0 (4.5–7.5 [2.0–10.0]; $p = 0.029$). Overall satisfaction was greater in the remifentanyl group ($p = 0.001$). Thirty minutes after delivery, infant neuroadaptive and capacity scores (NACS) were lower after pethidine than after remifentanyl, but there was no difference at 120 min (Blair et al. 2005).

1.4 Parenteral Opioids for Post caesarean Analgesia, with a Focus on Pethidine

In the past, opioids were commonly administered intramuscularly or subcutaneously because these routes of administration do not require the postoperative return of bowel activity or the use of sophisticated equipment (Gadsden et al. 2005). Intramuscular (IM) and subcutaneous (SC) medications are easy to administer, and associated with a long history of safety. However, there are some serious limitations to their use. First, drug administration requires injection, often repeated, which may be uncomfortable for many women. Second, there is large inter-individual variability in opioid pharmacokinetics and drug requirements. For instance, after abdominal surgery, C_{max} (peak concentration) and time to peak concentration varied almost five-fold in women given IM pethidine (Austin et al. 1980). There is also little correlation between body weight and blood concentration of pethidine, which makes estimating an effective dose regimen problematic (Austin et al. 1980). Furthermore, with IM administration, at C_{max} , the patient may have effective pain relief but have an increased incidence of unwanted effects, such as somnolence and sedation, whereas at lower concentrations, pain relief may be inadequate. (Gadsden et al. 2005).

In the post-caesarean section (CS) situation, PCA proves superior to IM administration. The American Society of Anesthesiologist's (ASA) Task Force on Acute Pain Management supports the use of IV PCA rather than IM opioid techniques for postoperative analgesia (ASA Task Force. 2004). Intravenous pethidine PCA is associated with better post-caesarean analgesia and less sedation than IM pethidine (Rayburn et al. 1988).

Patients receiving IM pethidine experienced a longer delay in sitting, walking and drinking after CS than patients receiving pethidine IV PCA (Cohen et al. 1991). A meta-analysis of 15 trials (Ballantyne et al. 1993) demonstrated better analgesia and greater patient satisfaction with PCA compared to IM pethidine. There were no significant differences between groups in the occurrence of side effects and trends towards less opioid use and shorter length of hospital stay with IV PCA were non-significant (Ballantyne et al. 1993). Walder et al in 2001 conducted another meta-analysis comparing opioid PCA with IM, SC, or continuous IV infusion. This showed better analgesia with no difference in opioid consumption or side effects (Walder et al 2001). A Cochrane meta-analysis conducted by Hudcova et al in 2006 compared IV PCA with conventional nurse administered opioid analgesia and demonstrated better postoperative analgesia and greater patient satisfaction with PCA, however greater opioid use, and a higher incidence of pruritus but not other side effects (Hudcova et al. 2006). Potential reasons for the different results observed include the use of different opioids (although approximately 70% of the studies used morphine), varied dosing regimens (e.g., dose, lockout interval, maximum allowable dose), variations in the timing of pain assessments, the use of different analgesic end points, and differences in therapies for breakthrough pain, nausea, and pruritus.

Figure-6 Comparison of VAS pain scores at 24-48 hours post CS: PCA versus control

(From Hudcova et al. 2006)

Several investigators examined various routes of administration or different opioids for post-CS analgesia. Sinatra et al, who evaluated IV morphine, pethidine and oxymorphone PCA at equipotent doses found no difference among groups in overall opioid use. However, more patients in the pethidine group had pain with movement (Sinatra et al 1989). In an important study Wittels et al demonstrated that nursing infants whose mothers received IV pethidine PCA after CS had greater neurobehavioural depression than nursing infants whose mothers received IV morphine PCA (Wittels et al 1997). This particular study involved elective and non-elective CS but there was no difference in the distribution of urgency for surgery among the groups after randomisation. Epidural anaesthesia was used and 4 mg of epidural morphine was administered to both study arms.

Figure 7 demonstrates the Neonatal Behavioural Assessment Scale (NBAS, score range 1-9) in four areas of neurobehavioural function; alertness, orientation to animate visual stimuli; animate auditory stimuli and orientation to both auditory and visual stimuli. For each neurobehavioural function the neonates studied were either bottle-fed or exposed to maternal morphine sulphate or pethidine.

Figure-7 Neonatal Behavioural Assessment Scale (NBAS) after Caesarean Section

Figure 1. Four neurobehavioral outcomes among three neonatal groups on the third day of life. Gray bars represent the proportion of neonates within each group that achieved a Brazelton Neonatal Behavioral Assessment Scale (NBAS) score of 1–3; cross-hatched bars represent the proportion of neonates within each group that achieved an NBAS score of 4–6; black bars represent the proportion of neonates within each group that achieved an NBAS score of 7–9. Four *a priori* outcomes of the NBAS (“alertness,” “orientation: animate visual,” “orientation: animate auditory,” and “orientation: animate visual and auditory”) are presented for each of the three neonatal groups. BTL = bottle-fed, MEP = exposed to meperidine in breast milk, MSO4 = exposed to morphine in breast milk. * $P < 0.05$ versus meperidine group, $†P < 0.05$ versus bottle-fed group.

Figure 2. Four neurobehavioral outcomes among three neonatal groups on the fourth day of life. Gray bars represent the proportion of neonates within each group that achieved a Brazelton Neonatal Behavioral Assessment Scale (NBAS) score of 1–3; cross-hatched bars represent the proportion of neonates within each group that achieved an NBAS score of 4–6; black bars represent the proportion of neonates within each group that achieved an NBAS score of 7–9. Four *a priori* outcomes of the NBAS (“alertness,” “orientation: animate visual,” “orientation: animate auditory,” and “orientation: animate visual and auditory”) are presented for each of the three neonatal groups. BTL = bottle-fed, MEP = exposed to meperidine in breast milk, MSO4 = exposed to morphine in breast milk. * $P < 0.05$ versus meperidine group, $†P < 0.05$ versus bottle-fed group.

(From Wittels et al. 1997)

Despite equivalent maternal PCA opioid use, nursing infants exposed to morphine were more alert and oriented to animate human cues on the third and fourth days of life than nursing infants exposed to pethidine. Even when PCA opioid requirements are reduced by prior administration of epidural morphine, post-CS PCA morphine is superior to PCA pethidine in the nursing parturient, because of preservation of neonatal alertness and orientation (Wittels et al. 1997)

The Wittels’s group conducted their pilot study in 1990, comparing clinical outcomes between the pethidine PCA and morphine PCA groups. Although the study was small and non-randomised, it confirmed the risk of pethidine induced neonatal depression in breastfed infants and suggested the superiority of morphine PCA for post-CS pain. All

elements of the infant NBAS scale were significantly lower in the neonates of mothers who received pethidine PCA (Wittels et al. 1990)

1.5 Epidural Pethidine

1.5.1 Pharmacology of Epidural Pethidine:

Cousins and his colleagues described epidural and intrathecal injection of pethidine for the relief of chronic and postoperative pain in patients with cancer. The term ‘selective spinal analgesia’ was coined to describe analgesia obtained without evidence of changes in sensory, sympathetic or motor function (Cousins et al. 1979). Glynn et al in 1981 published a study of epidural pethidine including 16 patients with either acute postoperative pain or chronic intractable pain. This study supported benefits from epidural pethidine for analgesia and the absence of neurological blockade (Glynn et al. 1981).

Following epidural administration, pethidine undergoes rapid absorption across the dura. The concentration of pethidine in cerebrospinal fluid (CSF) parallels the onset of analgesia, with maximum levels reached in 15- 43 minutes (Sjostrom S et al. 1987 and Nordberg et al. 1988). A similar fraction of a bolus of epidural pethidine (3.7%) crosses the dura compared with epidural morphine, but the rate of transfer across the dura is significantly faster with pethidine (Sjostrom S et al 1987). The absorption half-life across the dura varies from 2.7 to 14 min (7.6+-2.0 min). The CSF concentrations of pethidine are at all times higher than the concurrent plasma concentrations, with CSF: plasma ratios of 75, 135, 75 and 55 after 5, 60, 240 and 360 minutes, respectively. The mean pethidine CSF concentration at the time of request for supplementary pain relief was 1100 +- 260 ng.ml⁻¹(Sjostrom S et al 1987) .

Figure- 8 CSF and plasma concentration of pethidine until 6 hours post epidural injection

Mean pethidine CSF concentration (open circles) and plasma concentrations (filled circles) after epidural administration of pethidine 30 mg in the 6 hour study group (From Sjoström et al. 1987).

Pethidine is removed at a faster rate from CSF than is morphine after lumbar epidural injection. This reduces the potential for cephalad migration of drug and supraspinal adverse effects and explains why, unlike morphine, delayed respiratory depression is rare after epidural pethidine (Sjoström S et al. 1987). However some cephalad migration (towards the brain) does occur as shown by the presence of 1400-1650 ng/ml concentration in CSF samples taken at the level of the seventh cervical to the first thoracic vertebral level 10-60 minutes after lumbar epidural injection of pethidine 50 mg (Gourlay et al. 1987).

At 24 hours post epidural injection of pethidine 30 mg, the pethidine CSF concentration–time curves display a biphasic disposition process, with a slower phase between 8-12 and 24 hours after injection. The late half life averages 982 ± 449 minutes. CSF concentrations and the mean pethidine CSF concentration at the time of request of supplemental analgesia are similar to those noted at 6 hours post epidural injection (Sjoström et al. 1987)

Figure- 9 Mean CSF pethidine concentrations at 24 hours post epidural injection

Mean pethidine CSF concentrations after epidural administration of pethidine 30 mg in the 24 hours study (group V) (circles) and CSF concentration-time curve (From Sjostrom et al.1987).

Opioid lipophilicity (lipid solubility) is well correlated with the fraction of opioid present in the subarachnoid space after an epidural injection and how well the opioid binds to the neuronal tissues in the subarachnoid space. Instantaneous homogenous distribution of opioids in CSF is not likely after epidural administration. A compartmental model can only demonstrate gross changes and differences in drug kinetics, and does not differentiate between receptor-binding and nonspecific tissue binding in the subarachnoid space, nor between elimination to the blood and elimination by CSF bulk flow (Sjostrom et al. 1987).

Figure- 10 compartmental model of epidural pethidine and CSF fractions

Pethidine compartmental model. A1 is a sampling compartment (CSF) in the subarachnoid space, A2 is a tissue compartment in the subarachnoid space, K_a the absorption rate constant across the dura, and k_{12} , k_{21} and k_{10} are the transfer rate constants between the compartments and elimination from the compartment A1, respectively (From Sjostrom et al. 1987).

The analysis used by Sjostrom et al in 1987 suggests that epidural pethidine is removed from the CSF to a subarachnoid tissue compartment (i.e. nervous tissue) faster than is morphine (Sjostrom et al. 1987)

Figure- 11 compartment analysis of pethidine in the subarachnoid space after epidural administration

Compartment analysis of epidural pethidine (continuous line) and morphine (interrupted line). Fractions of pethidine and morphine in the two compartments, A1, (CSF sampling compartment) and A2 (tissue compartment), in relation to the total amount remaining in the subarachnoid space (from Sjoström et al. 1987).

Twelve hours after epidural injection, only 10% of pethidine is present in the CSF (the rest being transferred to the neural and fat tissue within the subarachnoid space). In comparison, 50% of epidural morphine is still present in the CSF at 12 hours after injection.

The total amount of epidural pethidine that remains in the subarachnoid compartment follows a similar pattern to that of CSF concentration curves. The curve shows a rapid peak of pethidine, followed by a more rapid decrease initially. From about 5 hours after injection, the relative amount of pethidine exceeds that of morphine, which supports the

theory that the spinal cord acts as an “affinity column” for lipophilic substances after spinal administration (Sjostrom et al. 1987; Yaksh 1981).

Figure- 12 Pethidine fraction in the subarachnoid space

Compartment analysis of epidural pethidine (continuous line) and morphine (interrupted line). Amounts of pethidine and morphine left in the subarachnoid space (corresponding to the amount in compartment A1 plus A2) related to the total amount of an epidural bolus passing to the subarachnoid space (From Sjostrom et al).

Vascular uptake occurs rapidly after epidural injection of pethidine. Peak concentrations occur within 10-15 minutes and the reported terminal elimination half life ranges from 124 to 324 minutes (Sjostrom S et al 1987, Nordberg et al 1988 and Husemeyer et al 1981). After epidural doses of 12.5 to 75 mg the peak plasma concentrations of pethidine were below the minimum effective analgesic concentration (MEAC) but exceed MEAC after 100 mg (Ngan Kee 1996).

The onset of analgesia is closely related to peak CSF pethidine concentration. Glynn et al demonstrated that patients with a high CSF/plasma ratio had complete analgesia. The

rapid rise in CSF pethidine concentration in the first 5 minutes coincided with the onset of analgesia.

Figure- 13 CSF and Plasma concentration of pethidine after 100 mg epidural injection of pethidine.

Range of CSF pethidine (---) and blood pethidine (solid line) concentrations for the eight patients studied after epidural injection of 100 mg of pethidine. The shaded area is the range of blood concentration associated with analgesia found in seven patients who were studied after IV pethidine (From Glynn et al. 1981).

The efficacy of a drug partly depends on its physicochemical properties, particularly its lipid solubility. For example, the amount of drug that is sequestered in the epidural fat is entirely dependent on the drug's octanol-to-buffer distribution coefficient (Bernards et al. 2003). Consequently, lipophilic drugs (e.g., fentanyl) with a high octanol-to-buffer partition coefficient in epidural fat may never reach the arachnoid membrane. Limited drug transfer across the meninges results in poor CSF bioavailability. To evaluate movement of opioids from the epidural to the subarachnoid space, Bernards et al used a

porcine model to continuously sample opioid concentrations in the epidural and intrathecal spaces. Using microdialysis techniques, the investigators measured the redistribution of epidural boluses of morphine, alfentanil, fentanyl, and sufentanil from the epidural space. Opioid concentrations were measured over time in the epidural space, subarachnoid space, systemic venous plasma, and epidural venous plasma. There was a strong linear relationship between lipid solubility and mean residence time, indicating that more lipid-soluble opioids spent a longer time in the epidural space. These drugs partition into the epidural fat, with ongoing slow release. Because of their long residence time in the epidural space, more lipid-soluble drugs are found in lower concentrations in the CSF and thus show decreased bioavailability to opioid receptors in the dorsal horn of the spinal cord (Santos & Bucklin 2009).

Another component of epidural opioid distribution is the proportion of drug absorbed systemically, thus exerting supraspinal effects. The method of epidural administration appears relevant. Administration of low concentrations of a lipophilic opioid e.g., fentanyl via an epidural infusion result in greater vascular uptake from the sequestered fraction in the epidural fat, thereby limiting drug access to the spinal cord (Coda et al. 1995 & 1999; Miguel et al. 1994). In contrast, when lipophilic opioids are administered by epidural bolus injection (Liu et al. 1996) or by epidural infusion of short duration (D'Angelo et al. 1998), they cross to CSF to exert primarily a spinal analgesic effect. Ginosar and coworkers compared the analgesic effects of epidural bolus injection and epidural infusion of fentanyl in human volunteers. Epidural fentanyl infusion produced analgesia by uptake into the systemic circulation with redistribution to the brain and peripheral opioid receptors. Epidural bolus administration of fentanyl produced analgesia by selective spinal mechanisms (Ginosar et al. 2003). These results were consistent with previous reports that an epidural fentanyl bolus results in a larger amount of fentanyl in the epidural space than occurs at any time during an epidural infusion, such that there is greater availability of drug to activate opioid receptors in the dorsal horn of the spinal cord.

Mode of action of epidural pethidine:

The observation that pethidine reached the spinal fluid in high concentrations very rapidly (Glynn et al. 1981; Tamsen et al. 1983) suggests that lipid soluble epidural

opioids may gain rapid access to the CSF via the arachnoid granulations in the dural cuff region, in addition to dural membrane penetration.

Figure- 14 spread of epidural opioids

Cross-section of the spinal cord and epidural space. Opioid spread in epidural space is depicted by white arrows and spread into CSF and spinal cord is depicted by black arrows. In dural cuff region posterior radicular spinal artery is readily accessible to opioid, and this artery directly supplies the dorsal horn region in the spinal cord (From Cousins& Bridenbaugh: spinal and epidural neural blockade).

This would permit facile access to the superficially located dorsal horn of spinal cord. It is possible also that a moderately lipophilic drug such as pethidine reaches the spinal cord by rapid uptake into the posterior radicular branch of the spinal segmental arteries, which run close to the dural cuff region. Vascular transport of opioids to the spinal cord is indicated by the similarity in onset time of analgesia after intrathecal and epidural administration. The rapid concurrent absorption of pethidine into the systemic circulation occurs via the extensive epidural venous plexus and then the azygos vein. Obstruction of the inferior vena cava, as occurs during pregnancy, may cause distension of the epidural veins and increased flow through the azygos vein (Cousins et al. 1984). This would result in an increased rate of systemic absorption of opioid from the epidural space, leaving less drug available for transfer across the dura to the spinal cord. Studies in women during labour support the hypothesis of more rapid absorption of pethidine

from the epidural space than seen in non-pregnant women (Gustafsson et al. 1981; Husemeyer et al. 1981; Husemeyer et al. 1982).

Figure- 15 venous drainage of the epidural space

Venous drainage of the epidural space into the inferior vena cava (IVC) via the azygos vein. Compression of IVC at 1, 2 or 3 results in rerouting of venous flow by internal vertebral venous plexus (epidural veins) to azygos vein. Increased intrathoracic pressure is transmitted to epidural veins and may result in increased flow up to the portion of internal vertebral venous plexus that is protected within the vertebral body (modified from Bromage PR: Epidural analgesia 1978).

Site and mechanism of action of epidural pethidine:

Since first described in 1979 (Wang et al. 1979; Cousins et al. 1979) neuraxial opioid administration has become a mainstay of obstetric anaesthesia and analgesia practice. Clinical and laboratory research has focused on the mechanisms of synaptic transmission as well as assessment of endogenous opioids and neurotransmitters that modulate this transmission (Santos & Bucklin 2009)

Pain perception involves a complex series of nociceptive transmissions that begin with stimulation of sensory nerves in the periphery, resulting in generation of action potentials within the spinal cord and synaptic transmission to supraspinal sites. Intraspinal administration of an opioid activates pain-modulating and pain-relieving systems that exist within the spinal cord.

Figure- 16 pain transmission in the spinal cord

Pain transmission in the spinal cord. Excitatory transmission occurs directly by release of amino acids such as glutamate (Glu) and peptides (sP [substance P], CGRP [calcitonin gene-related peptide]) and indirectly via activation of enzymes such as cyclooxygenase (COX) in nearby glia, which synthesize prostaglandins, including prostaglandin E₂ (PGE₂). Inhibitory mechanisms are primarily presynaptic, μ -opioid and α_2 -adrenergic receptors being the most common (or at least the most studied) (From Pan & Eisenach 2009; in Chestnuts' VI, 20: 39).

In early studies, Yaksh demonstrated that morphine could produce selective suppression of nociceptive processing without affecting motor function, sympathetic tone, or proprioception, when it was administered to the superficial layers of the dorsal horn of the spinal cord. However, when small amounts of opioid were administered to the cortex, the effects on nociceptive processing were negligible (Yaksh 1981). Collectively, this work demonstrated that small doses of opioid can be selectively administered to a receptor site (i.e., within the spinal cord) and produce profound analgesia. In contrast, systemic administration of a much larger dose of opioid results in activation of multiple central and peripheral receptors, resulting in both analgesia and a number of unwanted side effects.

All opioids produce analgesia by binding to G protein-coupled opioid receptors. Activation of opioid receptors subsequently inhibits both adenylate cyclase and voltage-

gated calcium channels. Inhibition of these calcium channels inhibits the release of excitatory afferent neurotransmitters, including glutamate, substance P, and other tachykinins (Eisenach 2001). The result is inhibition of ascending nociceptive stimuli from the dorsal horn of the spinal cord.

Opioid receptors are nonuniformly distributed throughout the CNS. Although parenteral opioids are most likely have both direct spinal and supraspinal effects, neuraxial opioids block the transmission of pain-related information primarily by binding at presynaptic and postsynaptic receptor sites in the dorsal horn of the spinal cord (i.e., Rexed laminae I, II, V). However, the rate and extent of neuraxial analgesia depend largely on the specific drug's physicochemical properties and the ability to reach opioid receptors in the spinal cord, as discussed previously (Santos& Bucklin 2009).

Figure- 17 Site of action of neuraxial opioids

Architecture of the spinal cord, showing the gray matter nuclei (*left*) and Rexed laminae (*right*). (From Ross BK, Hughes SC. *Epidural and spinal narcotic analgesia*. Clin Obstet Gynecol 1987; 30:552-65).

1.5.2 Clinical Applications of Epidural Pethidine in Acute Postoperative Pain:

The major clinical application for epidural pethidine has been the treatment of acute postoperative pain. In initial reports a dose of 100 mg given via a thoracic epidural catheter gave 4-20 hours of adequate analgesia in patient having cancer surgery (Cousins et al. 1979; Glynn et al. 1981). A number of other studies have compared epidural pethidine with IM and IV administration and found better analgesia, with lower drug requirements, after administration by the epidural route (Paech et al. 1994; Periss et al. 1990; Brownridge & Frewin 1985; and Ngan kee et al. 1997).

1- Single Epidural Bolus Injection:

Single bolus injections of epidural pethidine are an effective and safe method of analgesia after CS (Brownridge et al. 1981 & 1983). Doses were conveniently administered by nursing staff on general wards. The technique was particularly suited to this patient group because epidural catheters were commonly inserted for anaesthesia and midwives have experience managing epidural analgesia in labour and surgical wards (Ngan Kee 1998).

Two clinical trials compared the safety and efficacy of epidural pethidine 50 mg and IM pethidine 100 mg in patients following CS (Perris et al. 1990; Brownridge & Frewin 1985). Epidural pethidine had a faster onset of action and duration (2-4 hours) similar to the larger dose of IM pethidine. Ngan Kee et al demonstrated that pethidine 25 mg diluted in 5 mL of saline was superior to 12.5 mg but that bolus doses greater than 50 mg offered no improvement in the quality or duration of analgesia (Ngan Kee et al 1996). Epidural pethidine is not associated with marked haemodynamic effects (Ngan Kee et al 1997 and 1996). Paech et al evaluated the quality of analgesia and side effects produced by a single epidural dose of pethidine 50 mg or fentanyl 100 mcg. The onset of pain relief was slightly faster with fentanyl but the duration of analgesia was longer with pethidine (Paech 1989).

2- Continuous Epidural Infusion:

Epidural pethidine infused continuously is effective for analgesia after laparotomy and thoracotomy (Blythe et al. 1990; Slinger et al. 1995). Slinger et al compared epidural pethidine infusion with IV pethidine infusion, supplemented with PCA, after thoracotomy. Patients who received an epidural infusion had better analgesia, lower

drug consumption and improved postoperative pulmonary function compared with those patients who received IV pethidine.

Pethidine with local anaesthetic has been used after aortic surgery and shown to be comparable to fentanyl and bupivacaine combination (Cox et al. 1996). Personal experience at King Edward Memorial Hospital for Women in Perth, Australia, has shown that epidural pethidine premixed with 0.0625% levobupivacaine given via low thoracic epidural infusion is an effective method of analgesia after gynaecological cancer surgery.

3- Pethidine Patient-controlled Epidural Analgesia (PCEA):

The first report of pethidine PCEA after abdominal surgery was by Sjostrom et al. in 1988. They reported that analgesia with pethidine PCEA was satisfactory and qualitatively similar to that achieved with morphine PCEA (Sjostrom et al. 1988). Subsequently, Yarnell et al in 1992 compared pethidine PCEA with conventional IM pethidine and found that PCEA produced better quality analgesia despite lower drug consumption. It was preferred by both patients and the nursing staff (Yarnell et al. 1992). Similarly, Paech et al showed that 20 mg of pethidine via a PCEA device at 5 minutes lockout was clinically superior to pethidine IV PCA after CS (Paech et al. 1994). There were lower pain scores at rest and with coughing among those women receiving PCEA and sedation scores were higher in the group having IV PCA ($p=0.0001$). Ninety percent of this study population preferred the epidural route.

Figure- 18 VAS pain scores at rest in the two groups (cross over at 12 hours)

VAS pain scores at rest post caesarean delivery. PCIA versus PCEA groups with a cross-over of techniques (from Paech et al. 1994).

Figure- 19 VAS pain scores with coughing in the two groups (cross over allowed)

VAS pain scores with coughing post caesarean delivery. PCIA versus PCEA groups with a cross-over of techniques (from Paech et al. 1994).

Plasma concentration of pethidine and norpethidine were significantly lower in the PCEA group (Paech et al 1994).

Figure- 20 Plasma concentration of pethidine in the two groups

Plasma pethidine concentrations with the two techniques (cross-over allowed), demonstrating higher concentration during periods of PCIA use (from Paech et al. 1994).

Figure- 21 Plasma concentration of norpethidine 24 hours postoperatively in the two groups

Plasma norpethidine concentrations with the two techniques (cross-over allowed), demonstrating higher concentration during periods of PCIA use (from Paech et al. 1994).

Paech et al noted that systemic absorption of epidurally administered pethidine occurs during PCEA, indicating the possibility of a systemic contribution to analgesia during postoperative PCEA. Nevertheless, taken in conjunction with the clinical findings of their study, the plasma concentration data provided convincing evidence that the mechanism of analgesic action of epidural pethidine is principally spinal (Paech et al. 1994). Although the median plasma concentration of norpethidine at 24 hours postoperatively remained below the toxic range, rising levels were observed. This raises a concern about the safety of PCEA beyond 24 postoperative hours, because norpethidine concentrations might reach the toxic threshold. Ngan Kee et al found that that addition of 10mg/h background infusion to bolus pethidine PCEA conferred no analgesic benefits and increased drug consumption (Ngan Kee 1997).

Pethidine PCEA has been compared with fentanyl PCEA after CS in a crossover trial. After 24 hours patients had fewer side effects from pethidine and preferred pethidine to fentanyl (Goh et al. 1996). In another crossover study, Ngan kee et al randomised patients to receive pethidine or fentanyl by PCEA or IV PCA after CS, with crossover to the alternative route of administration at 12 hours. PCEA had advantages over IV PCA with both drugs and patients preferred PCEA over IV PCA with pethidine, although not with fentanyl (Ngan Kee et al. 1997).

Preservative-free morphine is perhaps the most popular adjuvant administered either intrathecally or epidurally in the US and many other countries. It provides effective and prolonged postoperative analgesia with a reduction in postoperative analgesic requirement. A meta-analysis of intrathecal opioid studies revealed that intrathecal morphine (0.1-0.2 mg) provided optimal analgesia with a median time to first request for supplemental analgesia of 27 h (range 11-29 h), in addition to reducing pain scores and the amount of supplemental analgesics needed for 24 h postoperatively (Dahl et al. 1999). Median time to first request for supplemental analgesia with intrathecal fentanyl was 4 h (range, 2-13 h), but the meta-analysis confirmed that neither intrathecal fentanyl nor sufentanil provides prolonged postoperative analgesia since they do not affect 24-h postoperative pain scores or consumption of supplemental analgesics when compared to controls (Dahl et al. 1999) A single dose of morphine administered epidurally has been shown to provide a postoperative analgesic duration of (18-26 h) similar to that of intrathecal morphine (Palmer et al. 2000 and Rosen et al. 1983).

In Australasia, it seems that pethidine PCEA for post-caesarean pain management is widely practiced in academic and tertiary maternity hospitals both for elective CS and for patients with a pre-existing epidural catheter, inserted during labour, but subsequently used for anaesthesia for non-elective CS. In Western Australia, a simple mechanical pump (Go Medical PCEA, Subiaco-WA) is widely used because of its ease and simplicity of use and cheap price. It is a single patient use pump. The disadvantages of the Go Medical PCEA pump are the fixed simple setting (4 ml of an injectate at 15 minutes lock-out), lack of the option of adding a background infusion and the potential of tampering with the device by patient and staff. Other pumps are available, however this pump is the most popular in this clinical setting in WA maternity institutions.

1.6 Basic Anatomy and Physiology of Human Lactation:

The breast is one of the few organs that undergoes most of its development postnatally. At birth the breast is represented by a nipple, a few small ductal elements and an underlying fat pad. Only with the onset of puberty and the secretion of oestrogen does the gland undergo a complex developmental process. Ducts grow out into the fat pad guided by an interesting structure, the terminal end bud (Daniel et al. 1987). This structure guides the elongation, branching and spacing of the ducts in women at the onset of menses. In rodents in which there is a significant luteal phase, alveolar structures begin to sprout from the sides of the duct stimulated by progesterone and probably prolactin. The mature breast resembles a flowering tree in springtime, with lobular alveolar complexes, called terminal duct lobular units (TDLU), which sprout regularly from the major ducts. The breast reaches a stage of quiescence marked by some waxing and waning of the TDLU, driven by the hormonal changes of the menstrual cycle (Schedin et al. 2000; Anderson et al. 1998; Bartow 1998; Andres & Strange 1999). The next stage of development begins in pregnancy. As the levels of progesterone, prolactin and placental lactogen rise, the TDLU undergo a remarkable expansion so that each lobule comes to resemble a large bunch of grapes. During mid-pregnancy, secretory differentiation begins with a rise in mRNA for many milk proteins and enzymes important to milk formation. Fat droplets begin to increase in size in the mammary cells, becoming a major cell component at the end of pregnancy. This switch to secretory differentiation is called *stage I lactogenesis* (Hartmann 1973; Neville et al. 2001). The gland remains quiescent but poised to initiate copious milk secretion around

parturition. This period of quiescence depends on the presence of high levels of circulating progesterone. When this hormone falls near to the time of birth, *stage II lactogenesis* or the onset of copious milk secretion ensues. As long as prolactin secretion is maintained and milk is removed from the gland, the mature function of the breast, namely milk secretion, is maintained. After weaning, the TDLU involutes with the apoptosis of a large proportion of the alveolar cells and a remodelling of the gland so that it returns to the mature quiescent state (Furth 1999)

Stage II lactogenesis in women

The top left panel in **Figure 22** shows the time course of the increase in milk volume that occurs during the first week postpartum (Neville et al 1988; Saint et al. 1984; Arthur et al. 1989). Milk transfer to the suckling infant starts at a volume of <100 mL/day on day 1 postpartum, begins to increase 36 hours after birth and levels off at an average of 500 mL/day around day 4. Milk composition also changes dramatically during this period, with a fall in the sodium and chloride concentration and an increase in the lactose concentration that starts immediately after birth and is largely complete by 72 hours postpartum (Neville et al. 1984). These changes precede the onset of the large increase in milk volume by at least 24 hours and are explained by closure of the tight junctions that block the paracellular pathway (Neville et al. 2001). Next, the concentrations of secretory immunoglobulin A and lactoferrin increase dramatically and remain high until approximately 48 hours after birth (Lewis-Jones et al. 1985). Their concentrations fall rapidly after day 2, in part because of dilution as milk volume secretion increases, but their secretion rate remains substantial (2–3 g/day for each protein, throughout lactation). Oligosaccharide concentrations are also high in early lactation, comprising as much as 20 g/kg of milk on day 4 (Coppa et al. 1999; Coppa et al. 1993), falling significantly to a level of 14 g/L on day 30.

Figure- 22 human breast milk composition and changes in the first week postpartum

The rate of secretion of milk volume and macronutrients in milk during the first 8 days postpartum. Data were derived from a study of 12 multiparous women who weighed their infants before and after every feed for the first 7 d postpartum and gave frequent milk samples. These data illustrate the high level of coordination required to produce milk of a consistent composition during early lactation. (From Neville et al 1988)

These complex sugars are also considered to have substantial protective effect against a variety of infections (Newburg 1996). Thus, during the first 2 days postpartum, large molecules with significant protective power dominate in the mammary secretion. The total nutrient value is low, simply because the amount of milk transferred to the infant is small. The substantial volume increase occurring between 36 and 96 hours postpartum is perceived as the ‘coming in’ of the milk and reflects a massive increase in the rates of synthesis and/or secretion of almost all the components of mature milk (Neville et al. 1991), including but not limited to lactose, protein (primarily casein) (Patton et al. 1986; Chen et al. 1998), lipid, calcium, sodium, magnesium and potassium (**Fig 22**).

Considering the secretion patterns of each of the milk components (Figure 22), the coordination achieved by the mammary epithelial cell among the activity of the various pathways that contribute all these different milk components is a marvel. So, “How is this remarkable degree of coordination achieved?” (Neville& Morton 2001)

Regulation of stage II lactogenesis

It has long been known that abrupt changes in the plasma concentrations of the hormones of pregnancy set lactogenesis in motion, although the precise hormones that accomplish the process have, in the past, been a subject of some debate. It is clear that a developed mammary epithelium, the continuing presence of levels of prolactin of approximately 200 ng.mL^{-1} and a fall in progesterone are necessary for the onset of copious milk secretion after parturition (Kuhn 1993). That the fall in progesterone is the lactogenic trigger is supported by evidence from many species. For example, exogenous progesterone prevents lactose and lipid synthesis in the mammary gland after removal of the source of progesterone, namely, the ovary, in pregnant rats (Kuhn 1969; Martyn & Hansen 1981), mice (Nguyen et al. 2001) and ewes (Hartmann et al. 1973). In humans; removal of the placenta, the source of progesterone during pregnancy in this species, has long been known to be necessary for the initiation of milk secretion (Halban 190; Neifert et al. 1981). Furthermore, retained placental fragments with the potential to secrete progesterone have been reported to delay lactogenesis in humans (Neiret et al. 1981). Thus, without a fall in progesterone, lactogenesis does not occur. However, other hormones must be present for this trigger to be effective. Either prolactin or placental lactogen are necessary for mammary development in pregnancy, and, with the fall in placental lactogen after removal of the placenta, prolactin is necessary for sustained lactation in most species. Bromocriptine and other analogues of dopamine (drugs that effectively prevent prolactin secretion) inhibit lactogenesis when given in appropriate doses (Neville & Walsh 1996; Kulski et al. 1978). Furthermore, prolactin was not necessary for lactogenesis in mice that had not yet given birth, the placental lactogen from the placenta providing the necessary stimulation of prolactin receptors (Nguyen et al. 2001). These data support the concept that a surge in prolactin is not the trigger for lactogenesis. It has long been known that glucocorticoids are necessary for milk secretion and lactogenesis, a postulate confirmed in laboratory mice (Nguyen et al. 2001). However, a surge of glucocorticoids is not necessary and a high dose of glucocorticoid does not promote lactogenesis. Insulin is generally required for induction and maintenance of milk protein gene expression in cultured mammary cells and glands, and deficiencies in plasma insulin lead to decreased milk production in rats and goats. However, a short-term deficiency in insulin does not interfere with lactogenesis in rats (Kyriakou & Kuhn 1973). Thus, the available evidence rules out acute changes in the

concentrations of prolactin, glucocorticoids or insulin as triggers for lactogenesis, although glucocorticoids and prolactin are necessary at some concentration for a fall in progesterone to act as the lactogenic trigger.

In summary, interpretation of the data available from both animal and human studies indicates that the physiological trigger for lactogenesis is a fall in progesterone, in the presence of sufficient prolactin and cortisol concentrations for the trigger to be effective. The caveat is, of course, that the mammary epithelium must be sufficiently prepared by the hormones of pregnancy to respond with milk synthesis. Postpartum prolactin levels are similar in both breast feeding and non-breast feeding women, so the basic process occurs regardless of whether breast feeding is initiated (Kulski et al. 1978). Similarly, glucocorticoids are necessary but their role is currently far from well-defined and, indeed, has received little study in the past two decades. Likewise, the role of insulin in vivo is not well-defined, although it is likely to be important in maintaining a metabolic state that allows flux of nutrients to the mammary gland (Neville & Morton 2001)

The role milk removal in the timing or extent of lactogenesis

A delay in the onset of lactogenesis has been reported with poorly controlled diabetes (Neville et al. 1988; Arthur et al. 1989; Neubauer et al. 1993) and stress during parturition (Chen et al. 1998). The mechanism is unknown but the delay correlated with high cord blood glucose and cortisol concentrations. The delay occurred in women who put the infant to the breast during the first 2 days postpartum, suggesting that poor milk removal is not the cause of stress-related delayed lactogenesis. In another study high breast milk sodium concentration on or before day 3 was observed in clinical situations in which the infant failed to latch on properly (Fig 22) (Aperia et al. 1979; Morton 1994).

Figure- 23 Milk sodium concentration in poorly nursing infants

Milk sodium concentrations in poorly nursing infants. Three mothers of full-term infants visited the clinic on day 3 of lactation complaining of poor milk production and problems with infant latch on. Milk samples were taken for measurement of sodium and the mothers were instructed to use a breast pump several times daily and to take small samples of milk daily, which were later brought to the clinic for analysis of sodium. Sodium concentrations in right and left samples are plotted. Note that once pumping was initiated the sodium concentrations declined with a time course similar to that in reference women, shown as a heavy black line (from Morton 1994).

These high sodium concentrations were related to impending lactation failure and could be reversed by the use of a breast pump to obtain effective milk removal. These observations suggest that milk removal and/or effective suckling are necessary to obtain junctional closure and potentially an increase in milk volume secretion, at least in some women. Evidence on this point is mixed. Careful evaluation of milk composition and breast-filling in non-breastfeeding women by Kulski et al. suggested that milk removal is not needed for the programmed physiological changes that bring about lactogenesis stage II (Kulski et al. 1978). In contrast, Chapman and Perez-Escamilla found that formula feeding before lactogenesis was associated with a delay in the perception of lactogenesis (Chapman & Perez-Escamilla 1999). Furthermore, the time of first feeding and the breast feeding frequency on day 2 postpartum were positively correlated with milk volume on day 5 postpartum (Chen et al. 1998), suggesting that milk removal at an early stage after birth increases the efficiency of milk secretion. In the last decade local factors dependent on milk removal have been implicated in the regulation of milk secretion during lactation (Peaker & Wilde 1996). The question is: “What are these local factors and when do their effects become apparent?” It is speculated that they are

present in high concentration in the scant prepartum secretion product from the breast and that if not removed early in the prepartum period, they contribute to inhibition of lactogenesis stage II, despite adequate hormonal changes. Although Kulski and co-workers were unable to detect any delay in the change in milk composition in their study of non-breastfeeding women, it is possible that even the small changes in the amount of milk remaining in the breast engendered by removal of 5 or 10 mL of secretion product per day by manual expression, could stimulate lactogenesis stage II (Neville & Morton 2001)

It seems practical to conceptualise the problem of failed lactogenesis as preglandular, glandular or postglandular (Morton 1994). An example of preglandular causes is a hormonal cause, such as retained placenta or lack of pituitary prolactin. Glandular causes might be surgical procedures, such as reduction mamoplasty or, possibly, insufficient mammary tissue. Postglandular causes would be any reason for ineffective or infrequent milk removal. This latter aspect has received insufficient attention. A neonatal intensive care nursery where careful correlation between early milk removal and subsequent lactation performance could be evaluated would be ideal for such a study. In such studies milk volume would be most easily measured in women who are using a breast pump to provide milk for their infants. Very small samples could be taken for determination of milk sodium and casein on a daily basis to allow a true distinction to be made between failure of tight junction closure and reopening of the junctions due to lack of milk removal. Such data would be valuable in determining how to manage the initiation of breastfeeding in mothers of sick infants as well as in sick mothers of well infants. It would also be of great value to determine, using techniques developed at the Hannah Research Institute in Ayr, Scotland in collaboration with Prentice et al. (Prentice et al. 1989), whether a chemical present in colostrum inhibits milk secretion, using an in vitro model system. Identification of such a chemical and precise measurement of its concentration could provide a new index for predicting which women are likely to have problems initiating stage II lactogenesis (Neville & Morton 2001).

1.7 Factors affecting lactogenesis and the initiation and duration of breast feeding:

Breast feeding is recognised as being one of the ‘most natural and best forms of preventive medicine’ (Yeung et al. 1981) and is promoted internationally as the preferred method of feeding for infants up to the age of six months (World Health Organisation-WHO, 1985). In Australia and other Western countries a marked decline in the initiation and duration of breast feeding was experienced from the 1950s through the 1970s. Thereafter, breastfeeding rates increased steadily to a plateau in the mid to late 1980s (Scott& Binns 1999).

At the beginning of the previous century, before the widespread use of infant formula, breast feeding or the use of a wet nurse was the most common way to feed an infant. There is evidence that most Australian newborns were breastfed before the 1940s. However, by the 1970s only 40–50% of babies were breastfed (Australian Bureau of Statistics 1997)

Since then the prevalence of breastfeeding has increased along with growing public awareness of the importance of breastfeeding. In 2004–05, 88% of children aged under 3 years had ever been breastfed, receiving breastmilk either exclusively, or as part of their diet in combination with breastmilk substitutes and/or solid food (Australian Bureau of Statistics 2007).

In America, breastfeeding initiation rates are currently higher than they have been since the mid-20th century. Data released by the Centre for Disease Control (CDC) in May 2008, indicates that the proportion of American infants who were ever breastfed increased to 77% among those born from the years 2005 to 2006. Therefore, the goal for the Healthy People 2010 initiative of a 75% breastfeeding initiation rate was met. Unfortunately, rising breast feeding initiation rates have not been accompanied by increased breastfeeding duration. The United States continues to fall far below the breast feeding duration goal of the Healthy People 2010 initiative, which is that 50% of mothers will be breast feeding at 6 months and 25% at 1 year. The latest statistics from the CDC indicated that in 2004, the rate of exclusive breastfeeding at 6 months of age was 11%, and the rate of any breastfeeding at 12 months was 20% (Thulier& Mercer 2009).

Breastfeeding has been, and continues to be, a popular area of research. Scott and Binns emphasised in their review in 1999 the need to separate, as two processes, the decision to initiate breast feeding and the duration of feeding. The factors associated with the

decision to breast feed are not necessarily the same as those which are predictive of duration. For instance, the professional care and advice received in hospital may affect the continuation of breast feeding but, given that most women make their choice of feeding method prior to falling pregnant, care and advice are unlikely to have any great effect on the initiation of breastfeeding. Mansback et al in 1991 suggested that the distinction between initiation and duration of breast feeding may allow for greater conceptual clarity and better predictive possibilities (Mansback et al. 1991). This issue has been a problem in many studies performed in a restrictive setting e.g., hospital, clinic or a non- community-based setting. This matter makes application of the results to the community at large (external validity) very difficult and likely to be misleading (Rutishauser& Carlin 1992). Persson in 1996 noted that studies which attempt to correlate the prevalence and duration of breastfeeding with possible determinants in society, such as the family, the mother or the infant, often fail to consider that the behaviour is multifactorial in nature (Persson 1996). Hence, a more comprehensive approach to the study of breast feeding determinants necessitates multivariate analysis of the data, which allows for simultaneous interpretation of association and interactions between variables (Scott and Binns 1999).

Factors affecting duration of breastfeeding and predictors of cessation of feeding:

The following table summarises all the relevant factors that may affect the duration of breastfeeding:

Table- 2 Variables that may affect breastfeeding duration

Demographic Variables	Biological Variables	Social Variables	Psychological Variables
Race	Insufficient milk Supply	Maternal work	Prenatal maternal intention
Age	Infant health problems	Support from significant others	Maternal interest
Marital status	Maternal obesity	Inconsistent professional support	Maternal confidence
Level of education	Physical challenges	Appropriate professional support	
Socioeconomic Status	Maternal smoking		
WIC status	Parity		
	Method of delivery		
Note: WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.			

(From Thulier and Mercer, 2009, *JOGNN*, 38: 259-268)

1.7.1 Demographic Variables:

A-Race:

There is wide variation in breastfeeding practice and duration of feeding among women of different races. In 2004, the CDC in the United States released data that showed that breast feeding rates at 6 months were highest among Asian women (16.1%), then White (11.7%), Hispanic (11.6%) and lowest among Black women (7.9%). Forste et al in 2000 analysed data from the National Survey of Family Growth for 1995, which had been collected by the CDC and included a national sample of 1,088 women of childbearing age. Researchers found that race remained a strong predictor of breast feeding, and that Black women were less likely to breast feed than non-Black women. Forste et al suggested that breastfeeding is as important as low birth weight when accounting for the race difference in infant mortality in the United States (ForsteR et al. 2001).

In Australia, there is some evidence to suggest that the feeding rates among migrants and Aboriginal mothers reflect the social norm (Scott and Binns 1999).

B- Maternal age:

Age is a strong demographic variable that influences breast feeding duration. Evers et al in 1998 studied influences on breastfeeding rates in communities in Ontario, Canada and found a positive association between breast-feeding duration and maternal age (Evers et al. 1998). Information from a comprehensive literature review that included multivariate analysis of data on breastfeeding initiation and duration also demonstrated a strong and consistent association between duration of breastfeeding and maternal age

(Scott & Binns, 1999). More recently, Dubois and Girard have conducted a longitudinal study in Quebec exploring the social inequalities that occurred in infant feeding during the first year of life. Their work, along with that of Kuan et al, confirms that maternal age is a predominant determinant of breastfeeding duration (Dubois & Girard 2003; Kuan et al 1999).

C- Marital status:

This demographic variable influences breastfeeding duration. Breastfeeding occurs more frequently among married women and married women breastfeed for longer periods of time (Evers et al., 1998; Kuan et al., 1999; Li et al, 2002). Callen and Pinelli completed a comparative literature review of studies published between 1990 and 2000, comparing differences in the incidence and duration of breastfeeding across Canada, the United States, Europe, and Australia. They consistently found that married women had a higher incidence and duration of breastfeeding (Callen & Pinelli J 2004).

D- Level of maternal education:

Educated women breastfeed more often and for longer periods of time (Scott & Binns 1999; Susin et al. 1999) (Figure 23).

Figure-24 Breastfeeding rates (a) by education level of mother —2001

(a) Includes babies breastfed exclusively, babies receiving breastmilk in combination with breastmilk substitutes, and babies receiving breastmilk in combination with solid food.

Source: ABS 2001 National Health Survey.

E- Socioeconomic class:

Women from lower socioeconomic groups show a lower incidence and decreased duration of breastfeeding (Coulibaly et al. 2006). Early cessation of breastfeeding is more common among low-income women (Dennis 2003).

1.7.2 Biological Variables:

A-Insufficient milk supply:

Women report insufficient milk supply as the most common reason for weaning of breastfed infants (Wambach et al. 2005). This problem is described as the mother feeling that her milk supply is inadequate to either satisfy her infant's hunger or to support adequate weight gain (Hill & Humenick 1989). The problem of insufficient milk supply has primary and secondary causes. A primary inability to fully lactate is related to anatomic breast abnormalities or hormonal aberration and affects up to 5% of women. Secondary causes of inadequate milk production are problems in breastfeeding management and these are much more common (Neifert 2001).

In response to inadequate supply, mothers most often provide their infant with supplemental formula or food. In clinical trials, early formula supplementation has been associated with shorter duration of breastfeeding (Li et al. 2004; Simard et al. 2005).

B- Infant health problems:

A negative association between infant health problems and both initiation (Ford&Labbok 1990) and duration of breastfeeding (LawsonK&Tulloch M 1995) has been reported after controlling for confounding factors. Health problems diagnosed at birth may prevent the early initiation of breastfeeding, often delaying it by 24 hours or more, and the management of health problems may necessitate the separation of infant from the mother, often for prolonged periods in the case of major problems.

However, Clements et al in a UK study (Clements M et al. 1997) and Ford et al in a New Zealand study (Ford et al. 1994) failed to find any association between admission to the neonatal intensive care unit and either the initiation or duration of breastfeeding. Similarly, Ford et al, Clements et al and Coreil and Murphy failed to demonstrate a negative association between the occurrence of perinatal health problems and breastfeeding duration (Ford et al. 1994; Clements et al. 1997; Coreil& Murphy 1988). These results suggest that a strong maternal commitment and a supportive

hospital environment can overcome intervening events that contrive to make breastfeeding difficult (Scott & Binns 1999)

C- Maternal obesity:

Obesity in women of child-bearing age has been increasing worldwide (Linne 2004). Maternal obesity is associated with a higher risk of hypertension, gestational diabetes and delivery complications such as prolonged vaginal delivery and CS (Linne et al 2004). The risk of preterm birth, shoulder dystocia and macrosomia rises progressively with the severity of maternal obesity (Cedergren 2004). Rasmussen in 2007 was able to demonstrate an association between women with high pre-pregnant body mass index (BMI) and the early termination of breastfeeding. Rasmussen theorised that excess maternal adipose tissue may interfere with the development of the mammary glands. Difficulty breastfeeding could also be related to hormonal and metabolic abnormalities associated with excess maternal adiposity, resulting in a delay in the onset of copious milk secretion (Rasmussen 2007). He also concluded that breastfeeding difficulties can occur as a result of preterm birth or birth of a macrosomic baby.

D- Maternal breast problems:

Women have reported that discomfort and disruption caused by sore nipples; engorgement, mastitis and plugged ducts are reasons for weaning (Simard et al. 2005; Wamback et al. 2005). Women who experienced difficulties with breastfeeding at or before 4 weeks postpartum were much more likely to wean before 6 months (Scott et al. 2006)

E- Maternal smoking:

Maternal smoking has been negatively associated with breastfeeding duration. Simard et al in 2005 in their Canadian study found smoking in the postpartum period was associated with an 8 weeks shorter breastfeeding period (Simard et al. 2005). A Brazilian study, after controlling for confounders, reported that children whose mothers smoked were 1.34 (95% CI 1-1.8) times more likely to not have been breastfed at 6 months (Hotra et al. 1997). Furthermore, a clear and significant dose-response pattern was present with the daily number of cigarettes smoked by the mother. Compared with non-smokers, mothers smoking 10-19 cigarettes presented an odds ratio of 1.16 (95% CI= 1-2.61) for breastfeeding for less than 6 months, while the odds ratio for mothers

who smoked 20 or more cigarettes daily was 1.94 (95% CI= 1.10-3.39). A similar pattern has been noted by other investigators (Ford et al. 1994; MacGowan et al. 1991).

F- Parity and prior breastfeeding experience:

Prior breastfeeding experience has been found to be a strong predictor of continued breastfeeding at 6 weeks postpartum (Hass et al., 2006). Li et al in 2002 in the Third National Health and Nutrition Examination Survey concluded that, while multiparous women were less likely to initiate breastfeeding, they were more likely to breastfeed for a longer duration (Li et al. 2002). De Lathouwer and colleagues found that, among the women discharged from the maternity ward with a healthy baby, among multipara the lack of any previous experience of breastfeeding is the greatest risk factor in early definitive cessation of breastfeeding. They concluded that targeting such women would make it possible to provide more support for them when they start breastfeeding, consequently avoiding early cessation (De Lathouwer et al. 2004).

Figure-25 early cessation of the breastfeeding

Early cessation of breastfeeding whilst still in the maternity ward (From De Lathouwer et al. 2004)

G- Mode of delivery:

Caesarean delivery may present a challenge to breastfeeding success. The impact of CS has been researched in different settings with varying results. These differences reflect the differences in populations and the influence of confounding factors that are often present in this situation (Berens P 2007, chapter 18: 355-67. Hale & Hartmann Textbook of Human lactation). The initiation of breastfeeding may be delayed because of hospital routine and clinical pathways for managing caesarean births, the mother may be uncomfortable and needing analgesia, the neonate may be unwell if the delivery was urgent, and a general anaesthetic may have been given, all factors leading to a longer period of mother-infant separation. Moreover, the woman who requests the controlled experience of elective caesarean delivery may have different expectations of motherhood that influence her decision about or commitment to breastfeeding.

Findings about the relationship between route of delivery and breastfeeding outcomes have changed over time. During the 1980s and 1990s, researchers concluded that delivering by caesarean could delay a woman from putting her baby to breast or interfere with her attempts to nurse (Chen et al. 1998; Da Vanzo et al. 1990; Samuels et al. 1985). Dennis et al in 2003 suggested that a negative association exists between CS and breastfeeding initiation, but not the duration once breastfeeding has been established (Dennis et al. 2003). Scott et al in 2001 conducted a prospective cohort study of 1,059 women to identify determinants of the initiation and duration of breastfeeding among Australian women. They found no correlation between route of delivery and breastfeeding. Women who delivered by CS in Australia were more likely to breastfeed for longer periods than were women who had delivered vaginally (Scott et al. 2001).

A Brazilian cohort study conducted by Victora et al in 1990, studied 4912 children who were born in 1982. The caesarean delivery rate among this cohort was 28%; more than two thirds of those operations were performed urgently. The authors found very similar breastfeeding initiation rates (92% in the vaginal birth and the emergency CS, and 93% among those children delivered via elective CS). However, continuation at six months was seen in 26% of those delivered vaginally, 29% of those who had undergone elective CS, but only 22% of those who had an emergent CS ($p < 0.05$) (Victora et al. 1990).

A smaller observational study in Turkey (Kakmak & Kuguoglu 2007), examined 200 mothers at admission to hospital, of whom 118 delivered via CS under general

anaesthesia and the remainder delivered vaginally. The authors used the LATCH tool (see later) for assessment of breastfeeding success. They found significant differences ($p < 0.01$) between the two groups at the first feed (6.27 for the CS group versus 7.46 for the vaginal birth group), and the third feed (8.81 versus 9.70 respectively). To examine influences relevant to CS, Kearney et al evaluated the average time to first breastfeed (Kearney et al. 1990), and breastfeeding outcomes in 121 primiparous women of whom 23% were delivered by CS. On average, these mothers first breastfed 11.1 hours after delivery compared to 4.5 hours for women delivering vaginally. There was, however, no difference between these groups in rates of weaning at 12 weeks or 6 months.

Rowe-Murray and Fisher reported similar findings in their Australian study of 203 primiparous women. Continuation rates at 8 months were not different despite initiation rates being lower in the CS group ($p < 0.001$) (Rowe-Murray & Fisher 2002).

Patel et al investigated the breastfeeding outcomes of women who had reached full cervical dilation in labour, but then required either CS or instrumental vaginal delivery (Patel et al. 2003). There was no difference in exclusive breastfeeding rates based on method of delivery. Seventy percent of women were exclusively breastfeeding at discharge from hospital and 44% at six weeks postpartum. Women delivered by CS were more likely to be exclusively breastfeeding at discharge and had a longer hospital stay (66% discharged day 0-4 versus 78% discharged day 5 or more).

As it seems that the timing of onset of breastfeeding is different between vaginal birth and emergency CS, Grajeda et al evaluated the timing of onset of breastfeeding. Primiparous women tend to have a later onset of lactation compared to multiparous women (5.4 h). Multivariate analysis found a significant association ($P = 0.04$) between parity/delivery mode and onset of lactation. Multiparous women (irrespective of mode of delivery) had earlier onset of lactation than primiparous women who underwent emergency CS. Likewise, primiparous women with vaginal deliveries tended to have ($P = 0.16$) an earlier onset of lactation than their counterparts who underwent an emergency CS (Grajeda et al. 2002).

The authors also studied salivary levels of cortisol to investigate an association between stress and delayed onset of lactation. A significantly higher cortisol level ($P < 0.05$) was detected in primiparous women compared to multiparae during and after delivery (figure 25). In this study, the authors found that the interaction of a stressful labour

(emergency CS), and primiparity was associated with a delayed onset of lactation. (Grajeda et al. 2002).

Figure- 26 salivary cortisol level before and after birth

Dewey et al followed 280 mother-infant pairs during the first two weeks of life (Dewey et al. 2003). They use the IBFAT assessment (see later) and defined suboptimal infant

breastfeeding behaviour (SIBB) as a score = 10. Mothers delivered by CS had both an increased risk of delayed onset of lactation (defined as > 72 hours) and their infants an increased risk of SIBB on the day of birth (day 0). The prevalence of SIBB was 49% on day 0, 22% on day 3, and 14% on day 7 and it was significantly associated with primiparity (days 0 and 3), CS (in multiparae, day 0), flat or inverted nipples, infant status at birth (days 0 and 3), use of non-breast milk fluids in the first 48 hours (days 3 and 7), pacifier use (day 3), second stage of labour > 1 hour (day 7), maternal body mass index > 27 kg/m² (day 7) and neonatal birth weight < 3600 g (day 7). Delayed onset of lactation (>72 hours) occurred in 22% of women and was associated with primiparity, caesarean delivery, second stage of labour >1 hour, maternal body mass index > 27 kg.m⁻², flat or inverted nipples, and birth weight > 3600 g (in primiparae). Excess weight loss occurred in 12% of infants and was associated with primiparity, long duration of labour, use of labour medications (in multiparae), and infant status at birth. The risk of excess infant weight loss was 7.1 times greater if the mother had delayed onset of lactation, and 2.6 times greater if the infant had SIBB on day zero (Dewey et al. 2003).

Evans et al studied the effects of CS on breast milk transfer to the normal term newborn over the first week of life (Evans et al. 2003). Eighty-eight mothers who delivered vaginally were compared to 97 delivered by CS. Milk transfer was assessed using test weighs prior to and after all feeds during the first 6 days of life. The first breastfeed occurred before 1 hour in 18.6% of mothers delivered by CS compared to 64.8% of those who had vaginal delivery. The mean breastmilk transfer (in mL/kg body weight) was consistently less during days 2-5 among mothers who had CS compared to mothers who gave birth vaginally. By day 6, there was no difference between the two groups. Of note in this study is that the two groups differed in parity, previous breastfeeding experience and time from delivery to first breastfeed, which may invalidate the authors' conclusions. Of the 97 women delivered by CS, 6 had general anaesthesia. These women were combined with those having regional anaesthesia, which could have skewed the results further. General anaesthesia is associated with lack of initial bonding between the mother and her infant (maternal postoperative pain, sedation and analgesic requirements) and secondly is more often used in emergency situations when fetal demise is likely if not delivered promptly. The latter alone may act as an inhibitor of lactogenesis II and consequent milk transfer.

Figure- 27 Milk transfer in vaginal birth and caesarean delivery

Profile of breast milk transfer (BMT) over the first six postnatal days to infants born by caesarean section (CS) or normal vaginal delivery (NVD) (From Evans et al. 2003).

H- Intrapartum stressors:

A certain amount of stress is normal when considering the events surrounding childbirth and the onset of lactation and is unlikely to have any detrimental effects. However, women and infants whose experience is at the high end of the range for stress may be at greater risk for adverse outcomes (Dewey K 2001). Stress can be categorised as primarily physical or physiological (e.g., pain and exhaustion) or primarily emotional (e.g., anxiety). It is not known whether the body's response to these two types of stress has different effects on lactation. At least two potential mechanisms can be hypothesised for the relationship between stress and lactogenesis. *Firstly*, as will be discussed in the next section, maternal stress seems to interfere with the release of oxytocin, the hormone that is responsible for the milk ejection reflex. If the milk ejection reflex is impaired often, the resulting incomplete removal of milk from the breast will eventually lead to down-regulation of milk synthesis. Although milk removal is not necessary to trigger lactogenesis stage II, it may be related to the timing of onset of full milk production or the volume of milk produced (Neville & Morton 2001; Chapman & Perez-Escamilla 2002). It is likely that maternal stress affects levels of other hormones involved in lactation, such as prolactin (Lau 2001), but there is little supporting evidence in humans (Chapman & Perez-Escamilla 2002).

Secondly, a newborn infant that experienced stress during labour may be too weak or too sleepy to latch on and suckle effectively at the breast. Even if the lactational

capacity of the mother is not compromised, this could lead to impaired lactogenesis if milk removal is not adequate. It should also be recognised that the causal pathway between maternal stress and lactogenesis could be reversed, i.e., mothers who experience delayed onset of milk production are likely to become stressed as a result. In observational studies it is often difficult to determine the temporal relationship between cause and effect (Dewey KG 2001)

Figure-28 various factors and their inter-relationship on the success of lactogenesis

Example of the inter-relationships among variables that may affect lactogenesis (From Dewey et al. 2001).

Maternal stress and the milk ejection reflex

Animal studies have demonstrated suppression of lactation after exposure to certain types of stressful stimuli (Lau 2001). In humans, Newton and Newton in 1948 conducted a novel study on a single breastfeeding mother and found that distractions interfered with the milk ejection reflex, but that milk transfer was restored when oxytocin was administered (Newton & Newton 1948). Later studies assessed maternal stress due to admission of their infants to the neonatal intensive care unit (Feher et al. 1989), and mothers who were given stressful task to complete and control women (Ueda et al. 1994). Both studies reached the same conclusion as Newton and Newton, which is that the milk ejection reflex is impaired by maternal stress.

Effects of stress during labour and delivery on lactogenesis

Chen et al in 1998 found that several markers of both fetal and maternal stress during labour and delivery (cord glucose concentration, duration of labour and maternal exhaustion score) were associated with delayed breast fullness, lower milk volume on day 5 and/or delayed casein appearance (the latter being a marker for the biochemical maturation of human milk). Dewey et al in 2001 also demonstrated that both mode of delivery (particularly an urgent CS) and duration of labour were associated with delayed onset of breast fullness (Dewey et al. 2001).

1.7.3 Social Variables:

A- Maternal work:

Maternal work outside the home is a critical variable that has a potentially strong influence on breastfeeding duration. In a study in the United States that focused on early maternal employment and child health and development, Berger et al noted that many mothers cease nursing once they return to paid work (Berger et al. 2005). Other studies confirmed a negative correlation between working and breastfeeding (Rea & Morrow, 2004). Scott et al determined that women who returned to work before 6 months were less likely to be fully breastfeeding at 6 months and less likely to be still breastfeeding at 12 months (Scott et al. 2006). Additionally, the amount of time a woman spends at work decidedly affects nursing. Women working full time demonstrated a marked decrease in breastfeeding duration (Taveras et al. 2003).

B- Support from significant others:

Support from significant others is a factor that contributes to breastfeeding success (Gill et al. 2007). In the cohort study by Scott et al positive associations were identified between a father's knowledge, attitudes and support and the likelihood of breastfeeding continuation. A trial involving 280 mothers and their partners in Italy was conducted to determine whether educating fathers to recognise the relevance of their role in the success of breastfeeding would result in more women initiating breastfeeding and an improved duration (Pisacane et al. 2005). Teaching fathers how to prevent and manage the most common lactation difficulties was associated with higher rates of full breastfeeding at 6 months. Most of the research on family relationships and breastfeeding, however, has focused on fathers' attitudes toward breastfeeding, not on the couple's relationship or family roles.

Women who stopped breastfeeding before 4 months postpartum reported significantly greater relationship distress than did women who continued to breastfeed. Distress in the couple's relationship undermined the mother's ability to attend to the demands of nursing. Mothers who reported that they were solely responsible for many household tasks were also more likely than other women to cease breastfeeding (Sullivan et al. 2004).

For many women, social influences extend beyond the father to the maternal grandmother and close friends. These groups also have the potential to influence women's feeding choices (Scott et al. 2006).

C-Inconsistent professional support:

In research studies worldwide, mothers have reported that inconsistent professional support has a negative influence on their breastfeeding efforts (Hall & Hauck, 2006; Nelson, 2007). In exploring the risk factors associated with breastfeeding duration, Taveras et al reported that a lack of skilled professional support was associated with decreased breastfeeding duration (Taveras et al. 2003). Many health professionals are inadequately prepared to provide prenatal education, perinatal support and postpartum follow-up for breastfeeding women (Wambach et al., 2005). Other investigators examined mothers' decisions to change from formula to mother's milk for very low birth weight infants. They found that at times, caregivers were reluctant to encourage mothers to initiate or continue to breastfeed for fear of making mothers feel guilty or coerced (Miracel et al. 2004)

Nelson in 2007 completed a study that investigated maternal newborn nurses and their experiences with breastfeeding women. Nurses in this study reported that inconsistencies in care were often related to a need for "buy in" of the newest recommendations, maternal need for individualised support and time constraints. Moreover, personal and professional experiences significantly influenced professional behaviour (Nelson 2007). In a longitudinal survey of 1,620 women in the USA, DiGirolamo et al assessed the perceived attitudes of health providers regarding breastfeeding and the relationship of these attitudes to women's breastfeeding experiences. Even a perceived neutral attitude toward breastfeeding among hospital staff was related to not breastfeeding beyond 6 weeks, especially among mothers who only intended to breastfeed for a short time (DiGirolamo et al. 2003).

D- Appropriate professional support:

Once breastfeeding has been initiated, professional support can improve the duration of breast feeding. In a study focused on the antecedents of breastfeeding duration, Perez-Escamilla et al in 1999 found that early supportive postpartum experiences in the hospital and during the first 2 weeks postpartum were associated with increased duration and length of exclusivity (Perez-Escamilla et al. 1999). Home visits from a public health nurse soon after births have also been shown to prolong lactation (Gill et al., 2007; Kang et al. 2005). Britton et al in 2007 conducted a Cochrane review of randomised controlled trials that compared extra support for breastfeeding mothers with usual maternity care. A total of 34 trials from 14 countries (29,385 mother-infant pairs) were included. The authors found that appropriate professional support resulted in considerable improvement in breastfeeding duration (Britton et al. 2007). Murray and co-workers calculated breastfeeding duration rates for all Colorado mothers during 2002 to 2003. Duration rates for recipients of baby-friendly hospital practices were compared with rates for the non-recipients of such practices. The duration was significantly improved when mothers experienced several specific hospital practices of the '*10 steps to successful breastfeeding*': nursing within the first hour, providing breast milk only, infant rooming-in, no pacifier use and referral to support after discharge (Murray et al. 2006). In Switzerland during 2003, Merten et al randomly sampled 2,861 mothers to analyse the influence of compliance with UNICEF guidelines on breastfeeding duration. Similar to the USA studies, they found that children born in baby-friendly health facilities were more likely to have longer breastfeeding duration. Thus, studies on duration of breastfeeding need to monitor the quality and quantity of professional support mothers receive, including whether or not the birth environment actively supports the breastfeeding mother-infant pair through evidenced-based practice (Merten et al. 2005).

1.7.4 Psychological Variables:

Several psychological variables are associated with breastfeeding duration, including prenatal maternal intention, interest in breastfeeding, and maternal confidence in ability

to breastfeed. Kronborg and Vaeth found that positive intent, attitudes and beliefs all increased breastfeeding duration (Kronborg & Vaeth 2004). In an Australian study to determine the factors associated with breastfeeding at 6 months postpartum, Forster et al reported that prenatal maternal intention and interest in breastfeeding were the most important factors determining the success of breastfeeding (Forster et al. 2006). Others report similar findings; Scott et al. (2006) suggested that maternal infant feeding attitude was a stronger independent predictor of breastfeeding initiation than socio-demographic factors. In an evaluation of predictors of continued breastfeeding, higher risk of breastfeeding termination was associated with shorter intended breastfeeding duration (DiGirolamo et al. 2005). Noel- Weiss et al conducted a randomised, controlled trial in a large tertiary hospital in Canada. Maternal confidence in the ability to breastfeed correlated positively with breastfeeding duration (Noel-Weiss et al. 2006). Over time, study findings are consistent: women at risk for premature cessation decided to breastfeed at a later stage of their pregnancy, demonstrate negative attitudes toward breastfeeding and positive attitudes about bottle-feeding, and have low confidence in their ability to breastfeed (Avery, et al. 1998; Dennis, 2003).

1.7.5 Miscellaneous Variables:

A-Early mother-infant contact:

To date, there are insufficient data supporting the value of early mother-infant contact on the establishment and duration of breastfeeding. Bernard-Bonnin concluded in his meta-analysis that early mother and infant contact positively influenced breastfeeding duration (Bernard-Bonnin 1989), but Perez-Escamilla et al conducted a more rigorous review of 14 studies on the effect of early contact on lactation success and concluded that the impact of early contact was unclear (Perez-Escamilla et al. 1994).

B-Rooming-in:

The practice of having the infant remain with the mother on a 24-hour basis while in hospital has been shown to be positively associated with lactation performance among primiparae, but only in the short-term. The theory is that this short-term impact of rooming-in on lactation success is a result of earlier initiation to breastfeeding and /or a much higher nursing frequency during the hospital stay, compared with other systems (Perez-Escamilla et al. 1992).

1.8 Effects of Epidural Analgesia on Breastfeeding:

This issue is much more complex than the effects of parenteral opioids on breastfeeding, partly because most of the studies conducted have been retrospective or prospective observational cohort studies and methodology has included telephone interviews post-birth. Few studies with adequate methodology have been performed. The next section examines the current evidence under two headings; the first discussing those studies in which no adverse effects were found, and the second discussing those studies finding an adverse effect. A discussion of some individual studies, with a critical review of their methodology and validity, is included.

1.8.1 Studies showing no negative association between epidural analgesia and breast feeding:

1-Abouleish et al 1978

This study involved 241 neonates delivered vaginally and selected randomly. In this study group either epidural (mepivacaine, lignocaine or bupivacaine), spinal or general anaesthesia had been administered. The control group consisted of infants delivered without anaesthesia. Each of the six groups was divided into breast- and bottle-fed subgroups. There were no significant differences in weight changes among the groups. The bottle-fed subgroup showed less weight loss than the breast-fed subgroup ($P < 0.05$). There was no interaction between the method of feeding and type of anaesthesia (Abouleish et al. 1978). This observational study was of simple design and did not include operative delivery. General anaesthesia was included as at the times it was used for vaginal birth. General anaesthesia may impact on lactogenesis differently.

2- Rajan et al 1994

The authors performed a postal survey of 1,149 patients in the UK; no patient notes were checked. This survey examined several other issues of obstetric care and its implications for outcomes and labour analgesia. The greater the obstetric intervention during labour and delivery, the less likely was a woman to be breastfeeding six weeks post-delivery. The authors could not examine the effect of labour epidural analgesia specifically on breastfeeding and attributed this to the method of data collection. They

reported that epidural lignocaine was associated with a positive effect on breastfeeding success. This was a retrospective study and no firm conclusions can be drawn as epidural analgesia could not adequately evaluated using this methodology.

3-Keihle et al 1996

The authors found no significant association between epidural use and early weaning (Keihle et al. 1996)

4- (Loftus JR et al 1995; Celleno D & Capogna G 1998; and Steinberg RB et al 1992)

These three studies investigated whether the concentration of the epidural local anaesthetic and opioid infusion during labour (up to 0.125% bupivacaine with fentanyl or sufentanil) had an effect on neonatal neurologic and adaptive capacity scores (NACS).

5-Halpern et al in 1999

This prospective study was based on telephone interviews of women who had given birth virginally to term infants. The women enrolled had expressed the desire to breastfeed prior to birth and gave birth in a very supportive hospital environment for breastfeeding. Women having epidural analgesia, parenteral opioid analgesia or no analgesia were compared. A logistic regression model was used to control for maternal age, previous breast feeding experience, induction of labour, mode of delivery, neonatal Apgar score at 5 minutes and the presence of meconium. Other variables of interest entered into the model included parenteral opioid within 24 hours of delivery, neuraxial fentanyl, neuraxial sufentanil, epidural lignocaine, epidural bupivacaine and duration of epidural analgesia. The authors concluded that there was no correlation between breast feeding success up to 6 weeks postpartum and the use of parenteral or epidural analgesia in labour. In the presence of strong hospital support of breastfeeding initiation from lactation consultants, with post-discharge follow up, these analgesic modalities did not appear to have adverse effects (Halpern S et al. 1999). This is one of the better-conducted studies in this field with logistic regression and numerous variables included in the model. However it suffers from a serious confounder, this being the strong intention of patients to breast feed and the strong hospital support for breast feeding. This study results may only apply to patients cared for in such an environment, where there is a strong culture of breast feeding.

6-Radzyninski 2002

The author conducted a small prospective study in women having vaginal birth and compared a cohort using epidural analgesia (an epidural infusion of a very low concentration local anaesthetic solution) to a cohort of unmedicated mothers. There was no significant difference between the two groups in relation to newborn behaviour, time the baby was held, and the time the baby latched on, the longest duration of sucking burst, sucking, swallowing and daily weight gain (Radzyninski 2002).

7-Riordan et al 2000

The authors collected birth and labour analgesia data from 3 hospitals. They evaluated 129 mother-infant couples up to 6 weeks postpartum. Breast feeding assessment was rigorous and these women were sub-divided into groups who were unmedicated, received IV analgesia only, epidural analgesia only or both the latter (Riordan et al. 2000).

Mothers who had no pain relief medication did not breastfeed significantly longer than those who were medicated. IBFAT breastfeeding scores in the epidural group were similar to those of the IV analgesia group (Figure 28). The IBFAT scores were then divided into three groups: low (0-4), medium (5-8), and high (9-12) and compared with the duration of breastfeeding. Dyads with low scores breastfed for a significantly shorter period of time than those with medium or high scores ($P < 0.001$). Spearman correlation was performed to determine if the mothers' feeding assessment scores were similar to those of the nurse observers and the scores of these two groups were positively correlated ($p < 0.0001$).

Figure-29 adjusted mean IBFAT scores by medicated group

Bar chart illustration of the various groups studied and correlating IBFAT scores (From Riordan et al. J Hum Lact 2000)

This trial used an objective assessment of breast feeding behaviour of the newborn. However; it was not randomised. The epidural group failed to demonstrate better scores than the group who had IV drugs.

8-Chang et al 2005

This prospective cohort study compared groups of women receiving epidural analgesia (continuous infusion) during labour and delivery (and no other types of analgesia) and unmedicated women. Effective initiation of breastfeeding and neonatal neurobehavioral outcomes were measured 8 to 12 hours after birth and to minimise age differences between infants, data collection took place within a 4-hour time frame. The 8-12 hour time frame was selected to coincide with the half-life of the epidural analgesic drugs and to fall within the critical period of initiating breastfeeding. Absence of breastfeeding difficulties and continuation of breastfeeding defined effective breastfeeding at 4 weeks of age. The time of follow-up was based on the known rapid decline in breastfeeding rate in the first 4 to 8 weeks and the feasibility of data collection (Chang et al. 2005)

In assessing the infant, in addition to the NACS, the investigators introduced the use of the LATCH-R score (Latching, Audible swallow of the baby, Nipple Type, Comfort whilst feeding, Help mother needed, and Responsiveness of mother to baby needs) and

investigated a correlation between the two methods of assessment of breastfeeding behaviour.

The neurobehavioral testing was done at a mean age of 9.6 ± 1.1 hours. The NACS scores ranged from 24 to 39, with a mean of 32.8 ± 3.1 . The breastfeeding observations were carried out at a mean age of 9.7 ± 1.2 hours. The LATCH-R total scores ranged from 5 to 12, with a mean of 10.0 ± 1.9 . The total feeding time ranged from none ($n = 8$) for those who did not latch or suck to more than 15 minutes ($n = 50$). There was no significant difference between the two groups in infant age at the time of neurobehavioral testing ($t = 1.35$, $P = 0.08$) or at the time of the breastfeeding assessment ($t = 1.49$, $P = 0.07$).

The correlation between the LAC score (0-6) (LAC being the first three components of the LATCH score) and the NACS score was significant (Spearman $\rho = 0.47$, $P = .01$). Using a one-sided t-test for independent groups, the mean NACS was compared between the groups demonstrating effective breastfeeding (LAC = 6) and ineffective breastfeeding (LAC < 6). At 8 to 12 hours of age, infants who breastfed effectively achieved a significantly higher score on the NACS (mean 34.2 ± 2.6 compared with 31.6 ± 3.0 ($t = 5.06$, $P < .001$)). Infants who were still breastfeeding at 4 weeks of age had a mean NACS score of 32.9 ± 2.9 at 8 to 12 hours of age and those who had already stopped breastfeeding at 4 weeks had a mean score of 31.7 ± 4.0 (not significant, $t = -1.3$, $P = 0.10$). The NACS score and primiparity accounted for 29.2% of the variance ($R^2 = 0.29$, $P < 0.001$) in LATCH-R scores. There was a positive relationship between the NACS total score and the LATCH-R score and a negative relationship between primiparity and LATCH-R score and this effect was protective (odds ratio = 0.71; 95% confidence interval, 0.60-0.83). That is, for every point increase in the NACS, the risk of ineffective breastfeeding at 8 to 12 hours of age was reduced by 29% (Chang et al. 2005). A criticism of this study is the authors' intention to correlate the NACS score to newly tested LATCH tool, because it was not adequately powered to assess an impact of epidural analgesia on the NACS score. To their credit the authors introduced the LATCH tool to this field of research and contributed greatly to its development.

9-Wislon et al 2010;

The authors studied all nulliparous women who requested epidural pain relief for labour at two tertiary maternity units. Women were not eligible if they had a contraindication to epidural analgesia, had undergone a previous epidural or spinal procedure or had received pethidine in the four preceding hours. All nulliparous women who planned to deliver at the trial centres had been sent study information at 34 weeks gestation and further information was given by the duty anaesthetist prior to obtaining written consent (Wilson et al. 2010)

No differences between groups were found in the time of first initiation of breastfeeding (Table 3).

Table -3 infant feeding by study group (post-delivery interview).

	Control n = 353	CSE n = 351	LDI n = 350	Non-epidural comparison n = 351	
Followed up	349	348	344	351 No pethidine 200	Pethidine 151
Initiated breastfeeding n (%)	231 (66.2)	230 (66.1)	217 (63.1)	132 (66.0)	84 (55.6)*†
Time to breast from delivery n (%)					
< 30 min	42 (12.0)	53 (15.2)	45 (13.1)	35 (17.5)	21 (13.9)
< 1 h	49 (14.0)	44 (12.6)	43 (12.5)	29 (14.5)	25 (16.6)
1–2 h	76 (21.8)	55 (15.8)	63 (18.3)	27 (13.5)	20 (13.2)
> 2 h	64 (18.3)	78 (22.4)	67 (19.5)	42 (21.0)	18 (11.9)

*Significance p = 0.002 vs Control.

†Significance p = 0.035 vs Non-epidural comparison (no pethidine).

CSE, combined spinal epidural; LDI, low dose infusion.

Duration of breastfeeding expressed as cumulative survival in weeks after delivery and estimated mean duration of breastfeeding in weeks for each study group. (From Wilson et al. 2010)

The mean duration of breast-feeding was not significantly different. Mean breastfeeding times for women in the epidural group and non-epidural, IM pethidine comparison group were similar. The overall mean breastfeeding survival time was 15.05 weeks (standard error 0.53 weeks, 95% CI: 14.01–16.09). There were no differences in the small proportions of women still breastfeeding at 12 months.

Figure-30 breastfeeding duration reported at 12 months presented as cumulative survival curve of breastfeeding.

Breastfeeding duration in the year following birth (From Wilson et al. 2010).

Table-4 Breastfeeding duration after birth by study group (12 month postpartum questionnaire).

	Control <i>n</i> = 353	CSE <i>n</i> = 351	LDI <i>n</i> = 350	Non-epidural <i>n</i> = 351	
Followed up	262	267	263	251 No pethidine 150	Pethidine 101
Breastfeeding duration; weeks					
Estimated mean	13.34	15.51	14.98	18.01	13.93
95% CI	11.41–15.27	13.47–17.54	12.90–17.06	14.93–21.10	10.82–17.03
Standard error	0.98	1.04	1.06	1.56	1.58
Still breastfeeding at 12 months <i>n</i> (%)	17 (6.5)	21 (7.9)	10 (3.8)	10 (6.7)	4 (4.0)

CSE, combined spinal epidural; LDI, low dose infusion.

Breastfeeding duration by study group (From Wilson et al. 2010).

1.8.2 Studies showing a negative association between epidural analgesia and breastfeeding:

1-Baumgarder et al 2003

Baumgarder et al conducted a retrospective cohort study of 115 parturients and their infants. These mothers had given birth vaginally under epidural analgesia and were compared to a matched cohort that did not receive epidural analgesia (Baumgarder et al. 2003).

Both epidural and non-epidural analgesia groups were similar except maternal nulliparity was more common in the epidural group. Two successful breast-feedings within 24 hours of age were achieved by 69.6% of mother-baby units that had had epidural analgesia compared with 81.0% of mother-baby units that had not (odds ratio [OR] 0.53, $P = 0.04$). These relations remained after stratification (weighted odds ratios in parenthesis) based on maternal age (0.52), parity (0.58), opioid use during labour (0.49) and first breast-feeding within 1 hour (0.49). Babies of mothers who had had epidural analgesia were significantly more likely to receive a bottle supplement while hospitalised (OR 2.63; $P < 0.001$), despite mothers exposed to epidural analgesia showing a trend toward being more likely to attempt breast-feeding in the first hour (OR 1.66; $P = 0.06$). Mothers who had epidural analgesia and who did not breast-feed within the first hour were at high risk of having their baby receive bottle supplementation (OR 6.27).

The authors concluded that labour epidural analgesia had a negative impact on breast-feeding in the first 24 hours of life even though it did not inhibit the percentage of breast-feeding attempts in the first hour (Baumgardner et al. 2003). This study design is biased by the fact that the epidural study group were women who had committed to having epidural analgesia prior to labour and who may have had different expectations of their care and breastfeeding success. The matched controls may have represented mothers who were against epidural analgesia and had different views of breastfeeding. In addition there were more primiparous women in the epidural group than the control group. Retrospective data collection has inherent problems with bias but highlights some associations between a problem and its possible cause, without implying causality. One conclusion of this retrospective study was that women receiving epidural analgesia are likely to be more comfortable during birth and consequently find it easier to commence breastfeeding early. The epidural group were also more likely to accept early bottle feeding, possibly because they are a group more accepting of interventions. In addition the frequency of feeds in a set period of time does not reflect the adequacy of breastfeeding, which is better assessed using milk transfer, test weighing and objective assessment methods.

2- Hendersen et al 2003

Henderson et al from the University of Western Australia examined prospective data from 992 primiparous women to examine the effects of intrapartum labour analgesia on breastfeeding duration (Hendersen et al. 2003). The subjects had been enrolled in a randomised trial investigating labour analgesia and delivery outcome, published in 2002. Women randomised had been allowed to change their mind about analgesia and 43.4% of subjects crossed over to the other group, a higher proportion changing to epidural analgesia. More than two thirds of the study participants who ultimately received epidural analgesia were compared with less than a third who did not. Those in the epidural group had a combined spinal-epidural (CSE) technique with epidural drugs self-administered via a PCEA device. Women in the other group had no analgesia, non-pharmacological methods of analgesia, nitrous oxide inhalation or IM pethidine analgesia. Follow up was at 2 and 6 months postpartum.

Table- 5 Demographic and obstetric factors associated with method of analgesia in labour and delivery

	Epidural (n = 690) n (%)	Other analgesia (n = 302) n (%)	P-value
Demographic factors			
Maternal age (years)†	26.5 (22.4, 30.9)	25.8 (21.8, 29.2)	0.023
Maternal education			
Post secondary	174 (25.7)	72 (24.3)	
Secondary or less	503 (74.3)	224 (75.7)	0.688
Smoking in pregnancy			
Smoker	155 (22.5)	72 (23.8)	
Non-smoker	533 (77.5)	230 (76.2)	0.682
Labour and delivery			
Induction of labour	355 (51.5)	98 (32.5)	<0.001
Syntocinon augmentation	204 (29.6)	29 (9.6)	<0.001
Duration of labour (hours)†	12.6 (9.3, 16.6)	7.9 (5.6, 10.8)	<0.001
Mode of delivery			
Spontaneous vaginal	268 (38.8)	251 (83.1)	
Operative vaginal	276 (40.0)	41 (13.6)	
Caesarean section	146 (21.2)	10 (3.3)	<0.001
Gestation (weeks)†	40 (39, 41)	40 (39, 40)	0.003
Birthweight (g)‡	3473 (460)	3324 (410)	<0.001

Total numbers may be less than 992 due to missing data. †Median (interquartile range). ‡Mean (standard deviation).

(From Hendersen et al. 2003)

Table- 6 Number of women still breastfeeding at 2 and 6 months-demographic and intrapartum data

<i>n</i> = 984†	2 months (<i>n</i> = 633)			6 months (<i>n</i> = 401)		
	<i>n</i> ‡	%	<i>P</i> -value§	<i>n</i> ‡	%	<i>P</i> -value§
Maternal age						
<25 years	211/405	52.1		112/405	27.7	
25+ years	422/579	72.9	<0.001	289/579	49.9	<0.001
Maternal higher education						
No tertiary education	427/727	58.7		246/727	33.8	
Tertiary education	199/246	80.9	<0.001	148/246	60.2	<0.001
Smoking during pregnancy						
None	510/755	67.6		352/755	46.6	
1–10/day	90/162	55.6		44/162	27.2	
>11/day	33/65	50.8	0.002	5/65	7.7	<0.001
Intrapartum analgesia						
None	86/110	78.2		57/110	51.8	
IMI pethidine	129/189	68.3		83/189	43.9	
Epidural	225/364	61.8		139/364	38.2	
IMI pethidine & epidural	193/321	60.1	0.003	122/321	38.0	0.039
Length of labour						
<12 h	368/549	67.0		232/549	42.3	
12+ hours	265/435	60.9	0.052	169/435	38.8	0.296
Mode of delivery						
Spontaneous vaginal	327/514	63.6		200/514	38.9	
Operative vaginal	223/315	70.8		148/315	47.0	
Caesarean section	83/155	53.6	0.001	53/155	34.2	0.014
Birthweight (g)						
<2980	98/142	69.0		58/142	40.9	
2980–3880	443/695	63.7		278/695	40.0	
>3880	92/147	62.6	0.437	65/147	44.2	0.639
Time to first breast-feed						
<1 h	295/409	72.1		187/409	45.7	
1–4 h	240/347	69.2		153/347	44.1	
>4 h	41/70	58.6	0.071	24/70	34.3	0.205

†No information about breast-feeding status of eight women. ‡Number (%) of women still breast-feeding at each interval. § χ^2 square or Fisher's exact test *P*-value where appropriate.

(From Hendersen et al. 2003)

In this study factors of maternal age < 25 years, lack of higher education and smoking during pregnancy were all significantly associated with cessation of breastfeeding at the time points selected. Univariate analysis showed intrapartum analgesia to be associated with breastfeeding at 2 and 6 months. At 2 months, 78% of women who had no analgesia were still breast-feeding, compared with 68% of women who had opioid analgesia, 62% of women with only epidural analgesia and 60% of women who received both forms of intrapartum analgesia ($P = 0.003$). Caesarean delivery was negatively associated with duration of breastfeeding ($P < 0.001$). Length of labour greater than 12 h ($P = 0.081$) and delayed time to first breast-feed ($P = 0.073$) were non-significant.

Breast-feeding duration was significantly longer in women who did not receive any pharmacological analgesia compared with women receiving opioid or epidural analgesia. Breast-feeding duration was shorter among those who received only opioid analgesia and shortest among women who received epidural analgesia in labour ($P = 0.036$). There was no significant additional effect on duration of breastfeeding among women receiving both methods of analgesia (Hendersen et al. 2003). To account for the

effects of CS and labour complications, multivariate analysis of women who had spontaneous vaginal delivery was performed (Table 7)

Table- 7 Results of Cox proportional hazards analysis: adjusted hazard ratios for shorter breast-feeding duration in the subset of women with spontaneous onset of labour and vaginal delivery†

Predictor	HR‡	95% CI	P-value
No epidural during labour	1.00	–	
Epidural during labour	1.44	1.04–1.99	0.029
No narcotic analgesia during labour	1.00	–	
Narcotic analgesia during labour	1.09	0.80–1.48	0.599
Maternal age (5 years increase)	0.805	0.695–0.932	0.004
Tertiary education	1.00	–	
No tertiary education	1.95	1.29–2.95	0.002
No smoking during pregnancy	1.00	–	
Smoking during pregnancy	1.79	1.32–2.44	<0.001

†Women with spontaneous onset of labour and vaginal deliveries only ($n = 484$). ‡Hazard ratios (HR) indicate the relative risk of a woman stopping breast-feeding at any time adjusted for all other variables shown. Factors with HR <1 indicate longer duration of breast-feeding; factors with HR >1 have an increased risk of stopping breast-feeding early.

(From Hendersen *et al.* 2003).

Epidural analgesia remained significantly associated with shorter breastfeeding duration (adjusted HR 1.44, 95% CI 1.04–1.99). Other significant factors were maternal age, tertiary education and smoking.

The effect of labour and delivery factors on the time and quality of the first breastfeed are shown in table 8 below. There were no differences in time to first breastfeed across analgesic groups.

Table- 8 Effect of intrapartum factors on the timing and quality of the first breast feed

	<1 h		1+ hours		P-value	Good quality [‡]	
	n	%	n	%		n	%
Intrapartum analgesia							
None	59	56.7	45	43.3	0.294	69	66.4
IMI pethidine	88	52.4	80	47.6		103	61.7
Epidural	144	47.4	160	52.6		195	63.9
IMI pethidine and epidural	121	47.4	134	52.6		148	56.1
Length of labour							
<12 h	254	52.0	234	48.0	0.091	315	64.3
12+ h	158	46.1	185	53.9		200	57.1
Mode of delivery							
Spontaneous vaginal	258	56.3	200	43.7	<0.001	286	62.5
Operative vaginal	130	49.6	132	50.4		166	62.4
Caesarean section	24	21.6	87	78.4		63	54.3

[†]No information about timing of first breast-feed and quality of first breast-feed from 161 and 152 women, respectively. [‡]Infant attached to breast well with good rhythmical sucking.

(From Hendersen et al. 2003)

The following are limitations of this study: Although the authors conducted an extensive analysis of the data, the subjects were primarily recruited and randomised into a trial in which the primary outcome of interest was birth outcome, not breastfeeding outcomes. The trial subjects were nulliparous women and the findings cannot be generalised to all parturients. The high cross-over rate in the trial was unfortunate but not surprising. As labour progressed more women felt the need for better analgesia and crossed over to the epidural group. This made testing for differences difficult (group size inequality) and compromised an ‘intention to treat’ analysis. No objective assessment of lactogenesis was conducted.

3-Beilin et al 2005

Beilin and his colleagues, in a randomised, controlled trial, examined the effects of labour epidural analgesia with and without fentanyl on infant breastfeeding (Beilin et al. 2005). The authors randomly assigned multiparous patients who had previously been successful in breastfeeding an infant for at least 6 weeks, into three groups. Patients were excluded if they did not intend to breastfeed, received intravenous opioids or had a CS. All patients received epidural analgesia for labour, those in group 1 (n= 60) receiving no epidural fentanyl (only epidural local anaesthetic), patients in group 2 (n =59) receiving a total dose <150 mcg epidural fentanyl, and patients in group 3 (n= 58) receiving > 150 mcg epidural fentanyl. The dosing was accomplished by adjusting the fentanyl content of the bolus doses and maintenance infusion. At 24 hours, the mother

and a lactation consultant did a global assessment of breast-feeding and filled out 9- and 12-item questionnaires, respectively, containing descriptors of breastfeeding problems at that time. The primary outcome of the study was breastfeeding difficulty at the time of initiation.

Using the tools described above, the authors found no difference between groups in the incidence of mild or moderate problems with breastfeeding ($P=0.09$). None of the patients had severe problems. Of the 21 items assessed by the mother and lactation consultant, only one was significantly different ($P=0.04$) among the study groups. This was likely a chance association, considering the number of comparisons involved. The sample size was sufficiently large to rule out an important clinical difference, defined by the authors as a 30% difference in the incidence of breastfeeding problems.

In the second part of the study, 157 of the original 177 subjects were interviewed at 6 weeks postpartum to determine whether they were still breastfeeding. It was found that women were less likely to continue breast-feeding if they had received > 150 mcg of epidural fentanyl during labour ($P=0.002$).

The criticisms that can be levelled at this study includes a relatively high proportion of patients (11%) for whom breastfeeding status was missing or unknown at 6 weeks: a breastfeeding assessment at 6 weeks that was not as precise as the one conducted at 24 hours postpartum; a possibility of unbalanced data between the groups in regard to families' attitude towards prolonged breastfeeding; and status of employment outside the home. Finally, there is no plausible physiological or pharmacological mechanism by which fentanyl might influence the incidence of breastfeeding at 6 weeks postpartum. In spite of these criticisms, Beilin et al have made a significant contribution to this field of research by publishing the first randomised controlled trial examining the effects of epidural fentanyl after birth (Halpern 2005).

4-Torvaldsen et al 2006;

Torvaldsen et al published the results of a prospective cohort study of 1280 women aged ≥ 16 years, who gave birth to a single live infant in the Australian Capital Territory in 1997 (Torvaldsen et al. 2006). Women completed questionnaires at weeks 1, 8, 16 and 24 postpartum. Breastfeeding information was collected in each of the four surveys and women were categorised as either fully breastfeeding, partially breastfeeding or not

breastfeeding at all. Women who had stopped breastfeeding since the previous survey were asked when they had stopped.

In the first week postpartum, 93% of women were either fully or partially breastfeeding their baby and 60% were continuing to breastfeed at 24 weeks. Intrapartum analgesia and type of birth were associated with partial breastfeeding and breastfeeding difficulties in the first postpartum week ($p < 0.0001$). Analgesia, maternal age and education were associated with breastfeeding cessation in the first 24 weeks ($p < 0.0001$). Women who had epidural analgesia were more likely to stop breastfeeding than women who used non-pharmacological methods of pain relief (adjusted hazard ratio 2.02, 95% CI 1.53, 2.67).

The authors concluded that women who had epidurals were less likely to fully breastfeed their infant in the few days after birth and more likely to stop breastfeeding in the first 24 weeks. They noted that although the relationship may not be causal, it was important that women at higher risk of breastfeeding cessation are provided with adequate breastfeeding assistance and support.

This study received extensive media publicity in Australia, presumably because it identified an association between epidural analgesia during labour and adverse breastfeeding outcomes. A critique of this study was provided by Camann (Camann 2007) and the opinions supported by Devore et al in a review article on the effects on epidural analgesia on breastfeeding (Devore et al. 2009).

The criticism of the Torvaldsen study includes, firstly, its misleading title, given it was a retrospective study with a secondary analysis, not a prospective randomised trial. Secondly, the patients' charts were not examined but data gathered through survey responses at 1, 8, 16 and 24 weeks postpartum, thus relying on recall. Analgesia used during labour was self-reported. The so-called epidural group was an amalgamation of pure epidural analgesia or epidural analgesia combined with other forms of pain relief (in most instances parenteral pethidine), and included women who underwent CS under either epidural or spinal anaesthesia, with or without prior labour epidural analgesia. Thus the authors did not discriminate between very different techniques of labour analgesia (with weaker solutions of local anaesthetic) and anaesthesia for CS (with very strong local anaesthetic concentrations), nor did they consider the type of delivery as a factor for breastfeeding success. The epidural solutions used were not described and it

was incorrectly assumed that all patients received a similar solution, based on a personal communication with a single anaesthetist (Devroe et al. 2009).

5-Various other small studies and retrospective analyses have concluded that fentanyl is responsible for reducing breastfeeding initiation and duration (Jordan 2006). It has been suggested that the dose of epidural fentanyl received in labour is associated with bottle feeding at hospital discharge and cessation of breastfeeding before 6 weeks postpartum (Jordan et al. 2005).

Summary of evidence of the association between epidural analgesia and breastfeeding:

To date, scientific evidence does not support a negative causal association between epidural analgesia and breastfeeding initiation. Most studies are either too restrictive, retrospective or inadequately powered. The Beilin study was of good design but its secondary analysis reached misleading conclusions. No clear evidence is currently available to confirm possible adverse effects of epidural analgesia on lactogenesis and human lactation.

1.9 Pharmacology of Drug Excretion in Breast Milk

1.9.1 Basic Pharmacological Principles:

The transport of lipids, proteins and electrolytes is controlled by the alveolar cell of the mammary gland, yielding milk with a uniform day to day composition. Electrolyte composition of human milk is tightly controlled once closure of the open-junctions between adjacent alveolocytes occurs, and the composition of this milk varies little during the course of lactation (Hale et al. 2007)

Drugs that are small and relatively lipid soluble pass from the blood across the alveolar epithelium and into the alveolar ducts largely by passive diffusion. Drug transfer into the milk compartment is thus largely controlled by the physicochemical properties of the drug, patient characteristics and by the other constituents of breast milk (Hale & Ilett 2002). In the first one to two days after birth when colostrum is produced, the junctions between adjacent epithelial cells are still open, allowing diffusion of both small drug molecules and large proteins through these junctions into the milk (paracellular pathway). As the junctions close (from day 2 onwards), passive diffusion (transcellular

pathway) becomes the predominant method for transfer of small lipid soluble molecules, including drugs. In general, large molecular weight drugs and proteins do not penetrate epithelial cells into milk in clinically relevant amounts (Hale et al. 2007)

Factors governing the doses received by the infant, and the plasma level achieved in the infant, are complex and may be considered under the headings of maternal pharmacokinetics; mammary pharmacokinetics and infant pharmacokinetics (Lee & Rubin 1993).

1.9i Maternal pharmacokinetics

The maternal plasma concentration of a drug, that is, its presentation within the breast for possible secretion in milk, depends upon its pharmacokinetics. Relevant factors are drug dose, route and frequency of administration, plasma protein binding, volume of distribution (VD), bioavailability, metabolism and clearance. Drugs with a high VD (i.e., highly lipid soluble drugs), are mostly distributed to the fat compartments outside the intravascular space, leaving only a small fraction of the drug available to transfer from plasma to breast milk. Highly protein bound drugs (e.g. ropivacaine versus lignocaine) have a smaller fraction of free (unbound) drug available for transfer (Lee and Rubin 1993).

Pregnancy leads to dilutional effects on plasma albumin concentration. Albumin binds to acidic drugs, such as salicylic acid and diazepam, so the free fraction of these weak acids increases towards term. The likelihood of a larger fraction of the drug being transferred into the breast milk increases with some neonatal side effects.

Drugs that are weak bases (e.g. most opioids) are not affected by the above change in plasma albumin, as they tend to bind to α -1 acid glycoprotein.

1.9ii Mammary pharmacokinetics

The milk to plasma (M/P) ratio of drug concentration may be used to estimate the dose of a drug in breast milk as a function of the maternal plasma concentration. It may be expressed in two ways: (1) the concentration in milk relative to that in plasma and (2) more accurately, the area under the concentration-time curve in milk relative to that in plasma. Such measurements depend on the transport mechanisms across biological

membranes, physicochemical properties of the drug, pH of milk and the distribution of the drug in milk (Lee and Rubin 1993).

Non-ionised (lipid-soluble) drugs enter the breast milk from maternal plasma by passive diffusion down a concentration gradient. Therefore the drug has to penetrate the capillary endothelium, the lipoprotein cell membrane, the myoepithelial cells and the mammary alveolar cell membrane to reach the milk compartment within the alveolar lumen of the breast.

The principal physicochemical properties of a drug that determine the extent of drug transfer into breast milk are its molecular weight, partition coefficient (distribution ratio in fat and water) and the degree of ionisation (pKa). Human milk has a relatively lower pH than plasma (7.09- 7.20 versus 7.35) (Ansell et al 1977) resulting in different drug dissociation and unequal total concentration of drug in the two media. As a general rule, weak acids achieve a lower concentration in milk than in plasma (M/P ratio < 1.0), whereas weak bases tend to have a larger fraction of the dose as 'non-ionised' in milk and hence achieve a higher M/P ratio (>1.0). Thus, drugs that are weak bases tend to be trapped in breast milk and confer a higher risk of delivery to the breast-fed neonate – this is termed 'ion-trapping' and is similar to the mechanism of transfer of drugs across the placenta during pregnancy.

Human breast milk is an emulsion of fat in water with lactose and protein in the aqueous phase. On entering the milk compartment a drug may bind to milk protein, partition into milk lipid or remain unbound in the aqueous phase. These three variable fractions constitute the total amount of a drug in a given volume of milk received by the suckling infant. The fraction of water and lipid content of human breast milk are the main determinates (being subject to change) of the amount of drug present in breast milk (Syversen& Ratkje 1985).

The lipid content is higher in milk than in plasma, and, consequently, drugs with great lipid solubility, including a number of anaesthetic drugs, tend to concentrate in the milk. In colostrum (1-3 days), the total fat content is on the average 29 g/l, while mature milk (> 30 days) contains 42 g/l. Thus, the amount of a drug with high lipid solubility might well be higher in mature milk than in colostrum. However, the total fat content also varies during a feed (less in the foremilk and more in the hindmilk), and during the day. (Spigset 1994)

The exposure of a suckling infant to a drug is not only related to the dose ingested in milk, but also depends on the infant's absorption, distribution, metabolism and excretion of the drug. In preterm and full-term newborns and infants, these pharmacokinetic parameters differ markedly from the corresponding values in children and adults (Spigset 1994).

In newborns and infants, the gastrointestinal peristalsis is irregular, and slow gastric emptying is a major determinant of the time course of drug absorption (Morselli 1976). The VD changes markedly during the neonatal period due to alterations in body composition (Friss-Hansen 1961), and differences in tissue and plasma protein binding (Green & Mirkin 1984). For several drugs, the VD per kg body weight tends to be larger in neonates than in adults, an example being lignocaine (Mihaly et al. 1978). These factors limit the interpretation of half-life ($t_{1/2}$) values and clearance should be the preferred method for comparing elimination capacity between children of different ages. However, most of the information in the literature is presented as half-lives. The infant's ability to metabolise the drugs differs both qualitatively and quantitatively from that of older subjects. For example, lignocaine has extensive liver metabolism (including first-pass metabolism) in adults, but in newborns, a considerable portion of the unchanged drug is excreted in the urine (Mihaly et al. 1978). Thus, the half-life of lignocaine is 2-3 times longer in neonates than in adults. The ability to perform conjugation reactions is very inefficient at birth. Drugs such as oxazepam, pethidine and morphine, which form active metabolites, have half-lives 3-4 times longer in neonates than in adults (Tomson et al. 1979)

1.9.2 Quantification of Drug Transfer into Human Milk:

Measurement of Drug Concentrations in Milk and Plasma

Measurement of drug concentrations in maternal plasma and/or milk provides useful information that assists in evaluating drug transfer to the infant. Maternal plasma concentrations of most drugs show wide intersubject variability as a result of varying doses and interindividual variability in clearance. As a matrix for drug assay, plasma is generally uniform and the accuracy and precision of measurements made by common analytical methods is good (Begg et al. 2002).

Breast milk can be thought of as a special tissue compartment linked closely to plasma. It is not surprising, therefore, that drug concentrations in human milk also show wide interindividual variability. Human milk is subject to significant time-dependent changes in lipid and protein content (Allen et al. 1991). In turn, these changes influence the extent of drug transfer into milk and may cause variability in the measurement of drug content. For example, drug assay precision at comparable concentrations is generally lower for milk than for plasma (Begg et al. 2001; Kristensen et al. 1999; Kristensen et al. 1998). The lipid content of breast milk is probably the cause of this variability, since it can vary two-fold and many drugs have significant lipid solubility. A comprehensive discussion of the problems of drug assay in human milk was published by Rossi and Wright in 1997 (Rossi & Wright 1997)

There are two general approaches to optimising the analytical procedures used to measure drugs in human milk. The *first* involves the validation of the assay method, mainly in terms of both recovery (the amount of drug that is successfully extracted from the milk) and precision (the reproducibility of the overall analytical procedure measured as the coefficient of variation [CV]) at extremes of milk composition. An example of this approach can be found in the quantification of naltrexone and its metabolite 6- β -naltrexol from human milk and sheep milk (Chan et al. 2001). Recovery and CV were similar over a wide concentration range, despite widely differing milk lipid contents (5% and 15%, respectively). This approach involves significantly more assay development time than is required for plasma. The *second* approach uses the “method of addition” in which individual breast milk samples are also used to construct the assay standard curve. Drug concentrations in milk are determined by taking 4 equal aliquots of each sample (with internal standard added), and spiking 3 of these with increasing concentrations of authentic drug standard. The samples are then extracted and analysed,

a standard curve (peak height ratio for “drug: internal standard” vs. “added drug concentration”) is constructed, and drug concentrations in milk are determined from the negative x -axis intercept of the plot. This method, which has been used widely in Emeritus Professor Inlet’s laboratories in Perth (Begg et al. 200; Kristensen et al. 2999; Kristensen et al. 1998; Hill et al. 2000; Wojnar-Horton et al. 1996; Wojnar-Horton et al. 1997; Rampono et al. 2000; Yapp et al. 2000), is very labour intensive, but it overcomes problems of analytical variability. Both of the above methods can yield quality data and the choice is pragmatically based on economic considerations.

Measurement of the Milk to-Maternal Plasma Ratio

The milk-to-maternal plasma (M/P) ratio gives an estimate of the distribution of drug between the maternal milk and plasma and provides an understanding of the mechanisms involved. In addition, the M/P ratio is used as an integral part of the calculation of infant dose (Wilson et al. 1985) according to equation (1):

$$(1) \quad \text{Infant dose} = \text{M/P} \times \text{Cav} \times \text{Vmilk},$$

Where;

Cav is the average maternal plasma drug concentration

Vmilk is the average daily volume of milk intake

Unfortunately, the M/P ratio may be misleading because it is subject to variability. Single paired milk and plasma concentration measurements have often been used to calculate the M/P ratio. However, this assumes that milk and plasma concentrations change in parallel, which is not necessarily the case, as illustrated for the antidepressant bupropion in figure below (Briggs et al. 1993):

Figure- 31 M/P ratio from single paired concentrations of a drug

Data for a single 100 mg oral dose of bupropion showing the drug concentration in plasma (solid circles) and breast milk (open circles), and milk-to-plasma ratio (M/ P) (solid squares) calculated from single points along a simple spline curve fitted to the data. An M/P of 4 also can be calculated by using the ratio of the area under the curve (AUC) for the milk-concentration time curve divided by that for the plasma-concentration time curve (From Briggs et al. 1993).

The M/P ratio at different time points can vary over a 2-3 fold range, as has been shown for sumatriptan (Wojnar-Horton et al. 1996), sertraline (Kristensen et al. 1994), paroxetine (Begg et al. 1999) and bupropion (Briggs et al. 1993). The problem of variation can be avoided by measuring the M/P ratio using measurements of the areas under the maternal plasma- and milk-concentration time curves (AUCs) after a single dose ($AUC_0 - \infty$) or over a dose interval (τ) at steady state ($AUC_0 - \tau$). Milk is not as easy as plasma to sample “instantaneously,” as sample collection takes time. In addition, milk production and composition can be highly variable and are dictated by infant-feeding patterns that cannot easily be simulated by expression. The average concentration for a complete expression of milk from both breasts is arguably the best representation of drug content (Begg et al. 2002).

The M/PAUC ratio itself may also be influenced by the method of calculation of AUC_{milk} . This can be achieved either by summation of rectangular areas under the concentration time curve (assuming the concentration measured represents the midpoint of the time between milk expressions) or by application of the log or linear trapezoidal

rule referenced to the end point of the collection period (Begg et al. 2002). A theoretical example of both methods is shown in figure below:

Figure- 32 Calculation of the Area Under the time-concentration curve

Simulated steady-state breast milk concentration data and cumulative excretion data for a dose of 20 mg to a 65 kg mother. The solid line with circles represents concentration versus time as a rectangular area plot. The dashed line with circles represents concentration versus time of collection as a line plot. The solid line with squares represents cumulative excretion versus time (From Begg et al. 2002)

In theory, the rectangular area method may be preferable when collection times are widely spaced. Compared to an AUC determined by rectangular area summation, the trapezoidal rule generally underestimates AUC in the absorption phase and overestimates it in the elimination phase. The overall difference in AUC between methods depends largely on the number of collections and the interval between them. Nevertheless, both methods generally give similar results.

There are other sources of variability in the M/P ratio. The variation in milk lipid content between foremilk and hindmilk (Hall 1975) has been shown to be associated with significant variability in M/P ratios for drugs such as doxepin (Kemp et al. 1985), dothiepin (Ilett et al. 1992), methadone (Wojnar-Horton et al. 1997) and paroxetine

(Begg et al. 1999; Stwoe et al. 2000). The extent of partitioning of drug into the lipid phase of milk is proportional to the drug's octanol: buffer (pH 7.2) partition coefficient (usually expressed as $\log_{10}P$) (Atkinson & Begg 1988) and it may be necessary to collect both foremilk and hindmilk samples for drugs with high $\log_{10}P$ values, to ensure that the concentration is representative. The number of samples (milk or plasma) that should be collected over a dose interval should also be considered. Generally, more samples are necessary for an $AUC_0 - \infty$ after a single dose than for an $AUC_0 - \tau$ at steady state. For drugs studied under steady-state dosing, collecting a minimum of 5 to 6 samples is sufficient (Begg et al. 2002).

Infant Dose

Calculation of Infant Dose

The main objective of studying drugs in human milk is to assess safety during breastfeeding. From the clinical perspective, it is the dose that the infant receives that is important, along with the resulting concentrations and the effects on the infant. The ideal assessment of infant exposure is the measurement of drug concentration in their plasma.

Calculation of Absolute Infant Dose

An informative and practical endpoint is the estimated dose received by the infant. In this context, it is important to estimate the "absolute" dose received by the infant:

$$(2) \quad \text{Absolute infant dose (AID)} = C_{\text{milk}} \times V_{\text{milk}}$$

Where;

C_{milk} = drug concentration in milk (C_{max} or C_{av}) expressed in mcg/L

V_{milk} = volume of milk ingested (L/kg/day)

The estimate of absolute infant dose involves measuring the actual amount (concentration $\times$ volume) of drug excreted in the milk from the time of ingestion of a single dose by the mother until the drug can no longer be detected in the milk (essentially to ∞). Alternatively, the amount of drug in the milk can be measured using

several collection times spread evenly between 2 consecutive maternal drug doses during a dose interval at steady state (i.e., regular dosing during chronic therapy).

As outlined above, a strategy of “total” milk collection at an appropriate number of fixed intervals (about 2 to 4 hours each) after the dose is preferred by many authorities (Begg et al. 2002). At the end of each collection interval, the sample volume is measured and an aliquot is reserved for the measurement of drug concentration. When appropriate, the remainder of the milk can be fed back to the infant. The total amount of drug (absolute infant dose) in each collection period is equal to the drug concentration multiplied by the volume of milk. The total (cumulative) dose can then be estimated by summing all the amounts for each period over the duration of the study (Begg et al. 2002).

Absolute infant dose estimated in this way represents a “maximum” dose. It is very likely that the infant may not always empty each breast. However, variations in infant suckling are likely to be in the direction of a lower dose. Thus, the maximum dose provides a safe yardstick. When it is not practical or possible to measure total available milk volume as described above, a strategy of collecting samples (10 mL) at intervals of about 2 to 4 hours can be used. For such a sampling protocol, Bennett recommended the use of an average milk intake value of 0.15 L/kg/day for the calculation of infant dose (Bennett 1996). Although this is representative of milk intake for a neonate, it may overestimate intake in an older infant who is also receiving supplementary feeding. Nevertheless, the infant dose calculated in this manner provides a generous (safe) estimate of absolute infant dose.

Jansson et al described using the average daily milk intake in their study of methadone excretion in breast milk (Jansson et al. 2007). They based their study on the original work of Neville and colleagues, who published on this topic in 1988 (Neville et al. 1988). This methodology allows the calculation of the absolute infant dose from one milk sample, using the average milk intake from the data in Neville et al’s original work.

Calculation of Relative Infant Dose (RID %)

The relative infant dose can be derived and compared with the dose received by the mother (usually as a percentage) after normalising the maternal dose to body weight:

(3)

Relative infant dose= Absolute infant dose (mcg/ kg/ d) x 100 ÷ maternal weight adjusted dose (mcg/kg/d)

Interpretation of Results

Because the breastfed infant is not supposed to be receiving any drug at all, a decision has to be made as to what dose can be considered safe. There are many factors to be taken into account, including the therapeutic index of the drug, any specific effects in children, the absolute dose, the duration of exposure and possible so- called dose-independent effects (e.g., hypersensitivity reactions).

Interpreting Absolute Infant Dose

When the drug has a recognised paediatric use, the absolute infant dose (as calculated above) can be compared directly to the normal therapeutic dose for an infant of that age (Begg et al. 2002). In the absence of such data/reference, the AID may be used as a baseline for comparison of later exposure via breast milk. Alternatively the first AID may be used to benchmark the safety of drug in the suckling neonate when used in breastfeeding mothers.

Interpreting Relative Infant Dose

For drugs that have no known inherent toxicity and are being taken by a mother at usual therapeutic doses, an arbitrary cut-off for infant dose has to be chosen. A relative infant dose of 10% of the weight-adjusted maternal dose is the most commonly accepted cut-off (Neville & Walsh 1999). Knowledge of the pharmacokinetics of the drug in the infant is also important, so that the plasma concentrations achieved after a given dose can be calculated as follows:

(4)

Drug concentration in plasma= (Absolute oral dose × Bioavailability) ÷ Clearance

Infants are born with immature clearance mechanisms and hence have lower drug clearance values (corrected for weight) than adults. In general, infant drug clearance is

particularly impaired in the premature neonate and increases gradually to adult levels after about 6 months. The clearance has been estimated to be approximately 5%, 10%, 33%, 50%, 66%, and 100% of adult maternal values at 24-28, 28-34, 34-40, 40-44, 44-68, and > 68 weeks post conceptual age, respectively (Begg 2000). The 10% relative dose cut-off applies to infants with “normal” clearance (compared to adults) and should be adjusted when there is impaired infant clearance.

Assessment of the Infant

Infant Plasma Drug Concentrations

Measurement of drug in the infant's blood is an excellent objective measure of drug exposure via milk. Ethical concerns and parental cooperation usually dictate that only one sample can justifiably be taken. A realistic approach to measuring infant concentrations is that any samples are a bonus. For drugs with long half lives and studied at steady state, it is probably unimportant to control the time at which infant plasma samples are taken in relation to the last maternal dose (Begg et al. 2002). The timing of infant blood samples for single-dose studies is more difficult, and a value judgment has to be made, after considering factors such as the profile of the milk concentration time curve, the milk ingestion pattern, and the likely drug $t_{1/2}$ in the infant. Infant blood samples should be drawn by an experienced paediatric phlebotomist, as this minimises trauma to the infant and also parental anxiety. The measurement usually gives parents an objective reassurance that their baby is receiving an acceptable drug exposure. Urine sampling in infants is of little use, as the result is qualitative and merely confirms the passage of drug through the infant. Analysis of the drug concentration in infant plasma/ serum often needs thoughtful consideration, because the small sample volumes available may raise the analytical limit of detection. Interpretation of measured drug concentrations in the infant can be made by comparison with known therapeutic concentrations in either adults or infants (Begg et al. 2002)

1.10 Assessment of Breastfeeding:

1.10.1 Clinical scores and assessment tools

Maternal perception of breast fullness

Maternal perception of the onset of lactogenesis-II (copious milk flow peripartum) may be a useful indicator of the beginning of copious milk flow. From a public health perspective, maternal perception of the timing of the onset of lactation may be a useful proxy for lactogenesis stage II because it describes when women actually feel their breast milk “come in.” The symptoms commonly reported to confirm the onset of lactation (Chapman and Perez-Escamilla 1999b) (i.e., breast fullness, engorgement, leaking) are consistent with the physiology of lactogenesis stage II and may indicate a milk supply that is more than adequate (Chen et al. 1998, Hartmann et al. 1996). Maternal perception is admittedly subjective, however; Chapman & Perez-Escamilla have studied this phenomenon in breastfeeding women post-CS (Chapman & Perez-Escamilla 2000). Women were randomised to a control group and to an electric breast pump group, assessed using maternal perception, test weighing and daily milk transfer, after which predictors of delayed onset and duration of breastfeeding were tested. The sensitivity and specificity of delayed maternal perception of the onset of lactation as an indicator of delayed lactogenesis stage II were 71.4% (20/28) and 79.4% (23/29), respectively. The positive and negative predictive values were 76.9 and 74.2%, respectively. The authors’ findings support that maternal perception of the onset of lactation is a valid, public health indicator of lactogenesis stage II. The determinants of low milk transfer at 60 hours postpartum and delayed perception of the onset of lactation are almost identical (Chapman & Perez-Escamilla 2000). Chen et al in 1998 evaluated four indicators of lactogenesis, including maternal perception of the onset of breast fullness (Chen et al. 1998). Although this term differs from Chapman’s definition of maternal perception, maternal/fetal stress markers were associated with delays in both breast fullness and casein appearance. The timing of the onset of breast fullness was highly correlated with milk volume on day 5 postpartum and with casein appearance. Delayed lactogenesis was demonstrated among primiparous women (vs. multiparous) by both delayed breast fullness and decreased milk volume on day 5. Chen and colleagues cautioned that maternal perception of breast fullness may not always be a useful indicator of lactogenesis, especially in situations where decreased breastfeeding frequency may result in engorgement (Chen et al. 1998).

Infant breastfeeding tool (IBFAT)

The IBFAT is a short assessment and measurement of infant breastfeeding competence (Matthews 1988; 1991). The IBFAT represents four major components of infant breastfeeding behaviour: (a) readiness to feed, (b) rooting, (c) fixing, and (d) suckling. The range of scores for each of the four components is 0-3. A total score can range from 0 to 12, with 12 being the score for vigorous, effective suckling. The instrument was based on observations in clinical practice, knowledge obtained from a literature review and consultation with experts in nursing and child development. The IBFAT also measures the mother's perception of, and satisfaction with, the feeding. Matthews (1988) found that inter-rater reliability between mothers' and researchers' assessments was 91%. Subsequent research indicates that mothers who reported low breastfeeding satisfaction are mothers of infants who were rated low on the IBFAT (Goer et al. 1994)

The mother-baby assessment tool (MBAT)

The Mother-Baby Assessment Tool is meant to assess the process of learning to breastfeed. It divides the process of breastfeeding into five steps: (a) signalling, (b) positioning, (c) fixing, (d) milk transfer, and (e) ending (Mulford 1992). For each step, there is both a mother and an infant behaviour; based on the assumption that breastfeeding is a mutual effort. Ten is the highest possible score: 5 for maternal behaviours and 5 for infant behaviours in each of the steps indicates a highly effective feeding. No evidence of reliability or validity of the MBA has been published.

The LATCH Tool

LATCH is a breastfeeding charting system that provides a systematic method for gathering information about individual breastfeeding sessions (Jensen et al. 1994). The *LATCH* assessment tool was developed to identify areas of needed intervention and to determine priorities in providing patient care and teaching. Because not all breastfeeding events can be observed by the hospital staff, mother-reported scores are recorded for continuing assessment. The system assigns a numerical score, (0, 1, or 2) to five key components of breastfeeding for a possible total score of 10. Each letter of the acronym *LATCH* denotes an area of assessment. "L" is for how well the infant latches onto the breast. "A" is for the amount of audible swallowing noted. "T" is for the mother's nipple type. "C" is for the mother's level of comfort. "H" is for the amount

of help the mother needs to hold her infant to the breast (Jensen et al. 1994). A score of 2 on each criterion meets the description of effective breastfeeding. The LATCH system has been found to have high inter-rater reliability (85.7%-100%) (Adams & Hewell 1997) and construct validity (Riordan et al. 2001). An R component, which measures the mother's responsiveness to infant cues and confidence to breastfeed, was added by the Winnipeg Regional Health Authority.

Chang & Heaman examined the effects of labour epidural analgesia on breastfeeding. They used the LATCH-R system and investigated how that correlates with the infant's behaviour based on the NACS (Neurologic and adaptive capacity score) (Chang & Heaman 2005). A positive relationship was found between neonatal neurobehavioural status and effective breastfeeding at 8 to 12 hours of age. Thus routine neurobehavioural assessment may be useful in identifying infants who are more likely to have difficulties with breastfeeding. Early recognition of mother-baby pairs who have more difficulties achieving effective breastfeeding will help prevent breastfeeding problems and early cessation of breastfeeding (Change & Heaman 2005).

The LATCH tool has also been used to predict the duration of breastfeeding. Kumar and colleagues studied the likelihood of continuing breastfeeding by collecting the LATCH data in an observational study of 18 mother-infant pairs (Kumar et al. 2006). They found that the 16-24-hour LATCH score had the highest AUC (0.72), with sensitivity of 75.0% and specificity of 63.2%. The RR (Risk Ratio) of a LATCH score of 9 or more at 16 to 24 hours was 1.7 (CI 1.1-2.7), $P = .004$. This means that women with a maximum LATCH score of 9 or more in the 16-24-hour period were more likely to be still breastfeeding at 6 weeks, compared to women with lower scores (Kumar et al. 2006).

Figure- 33 Receiver Operator Characteristics (ROC) Curve for LATCH tool

Receiver operating characteristic (ROC) curve for 16- to 24-hour LATCH score. AUC = area under the ROC curve (From Kumar et al. 2006).

Neurologic and adaptive capacity score (NACS)

The Neurologic and Adaptive Capacity Scoring (NACS) tool is not a pure breastfeeding assessment tool; however, it has been used by many authors to assess the neuro-behaviour of the newborn baby; in the context of its ability to breastfeed whilst under the potential influence of maternally-administered medication that could well be transferable into breast milk. The NACS was first used for neonatal neurobehavioural assessment (Amiel-Tison et al. 1982). Twenty criteria evaluate 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes, and general neurologic status. Each criterion is given a score of 0 (absent or grossly abnormal), 1 (mediocre or slightly abnormal), or 2 (normal), with a maximum possible score of 40. The NACS has demonstrated 92.8% inter-observer reliability (Amiel-Tison et al. 1982). Chang & Heaman rated 10 newborns using the NACS and achieved high inter-rater reliability ($r = 0.982$, $P < .01$). Among the 3 widely used neurobehavioural tests that assess the effects of maternal medication on the neonate, the NACS has been chosen by many investigators because it requires no complicated equipment, is not aversive or noxious to the neonate or the mother, is quickly observable and easy to score (Chang & Heaman 2005). Neurologically vigorous neonates were defined as those neonates who received a

total score of 35 to 40 (Amiel-Tison et al. 1982). Limitations of NACS are, first; its difficult to interpret, especially in the absence of controls, but confidence intervals overlapped with the arbitrary normal mean score of 35 (the normal range has never been determined) (Amiel-Tison et al. 1982). Second, it has been criticised because of poor test reliability (Helpern et al. 2001)

1.10.2 Objective and biochemical indicators of lactogenesis

Test weighing:

Test weighing has become the standard method of measuring maternal milk production (volume of milk removed from the breast either by the infant or by expression). Test weighing involves measuring the weight of either the mother or the infant before and after a breastfeed and taking the difference in weight as an indication of the amount of milk consumed (Daly & Hartmann 1995). Weighings throughout the feed may also be employed to discern the pattern of milk transfer throughout the breastfeed (fractional test weighing) (Woolridge et al. 1985). Any weight difference between weighings will necessarily include the evaporative water loss of the weighed person across that time period. If not corrected for, this can account for an error of up to 10-15% (Hartmann & Arthur 1986; Arthur & Hartmann 1987). However, a correction for evaporative water losses can be made by including a third weight measurement to measure the approximate rate of evaporative water loss of the weighed person. With the inclusion of this correction factor and the use of sensitive electronic balances, test weighing is a highly accurate method of determining milk transfer between mother and infant (Arthur & Hartmann 1987). As the amount of milk consumed at each feed and the time interval between feeds are highly variable, test weighing needs to be conducted at each feed, over periods of 24 hours or more, for accurate calculation of milk production (Woolridge et al. 1985; Hartmann & Saint 1984). Test weighing has been criticised by some for being costly, invasive and inapplicable in the community setting (Chapman & Perez-Escamilla 2000). The amount of milk production estimated by test weighing is theoretically similar to the total amount of milk synthesised during that period if the infant intake of breast milk is normal (Daly & Hartmann 1995). However, test weighing is not measuring the mother's ability to synthesise breast milk. Thus, an infant with a low appetite consumes little milk from its mother and this will be observed as a low milk production by test weighing. The mother's actual potential for milk production

may be several folds higher. Therefore, test weighing can not discriminate between an infant's ability to consume milk and the mother's ability to synthesise it (Daly & Hartmann 1995). In other words, test weighing allows an actual measurement of the milk transfer that occurred from the mother to her infant during breastfeeding, rather than the amount of milk that the mother produced or could produce.

Oxford flowmeter:

The Oxford flowmeter is composed of a miniature Doppler ultrasound flow transducer moulded into a thin latex nipple shield (Woolridge et al. 1982). Studies using the Oxford flowmeter have provided valuable information regarding the rate of milk transfer within a breastfeed. However, it provides a less accurate measure of the total milk transfer at a breastfeed than test weighing (Woolridge et al. 1985).

Swallow counting:

Simply counting the number and pattern of swallows may also be an accurate method for determining both the milk intake at a breastfeed, together with the pattern of milk transfer within that feed. Swallow counting may be considerably less invasive, as an approach for estimating that pattern of milk transfer at a breastfeed, than either the Oxford flowmeter or fractional test weighing (Lau & Henning 1989).

Isotope dilution method:

This method involves the dilution of stable isotopes of water within the mother and/or infant. These methods allow the unobtrusive measurement of the milk intake (Coward et al. 1979) and the calculation of the energy budgets of breastfed infant (Lucas et al. 1987).

Breast volume measurement:

The principle of this method is that in between breastfeeds the rate of increase in breast volume can be measured. This method is able to measure the short term rate of milk synthesis. Daly et al in 1992 have described a 'computerised breast measurement' (CBM). This was validated by comparing the change in breast volume at a breastfeed to the amount of milk consumed by the infant, as judged by test weighing. The close relationship observed between the change in breast volume and milk removal indicates

that changes in breast volume can be used to make accurate determinations of changes in the volume of milk within the breast (Daly et al.1992).

Figure- 34 the relationship between breast volume and amount of milk removal

The relationship between the volume of milk removed by either breastfeeding (and measured by test weighing) or expression and the change in breast volume at that breastfeed/expression (measured using the CBM system). The linear regression $y=1.14x-7.51$ ($r^2=0.86$, $p<0.001$, $n=257$; 95% CI for the slope: 1.09-1.2) describes this relationship (from Daly et al 1992).

Kent et al from the human lactation group at the University of Western Australia have studied milk production in women who breastfed for prolonged periods (Kent et al. 1998). They found a close correlation between milk yield and breast volume using the computerised breast measurement (CBM) system.

Biochemical indicators:

The biochemical contents of breast milk show a close correlation to the time of onset of copious milk flow i.e. lactogenesis-II (Peaker& Linzell 1975; Kulski& Hartmann 1981; Neville et al. 1986). Arthur et al from the University of Western Australia studied the validity of using biochemical markers of lactogenesis II in relation to breast volume and milk yield (Arthur et al. 1989). They demonstrated a consistent increase in the average concentration of lactose, citrate and glucose in milk from non-diabetic mothers with time after birth. There were significant increases ($p<0.05$) in the concentration of lactose and citrate between day 1 and day 2 after birth. For glucose, the first significant increase in concentration occurred between day 2 and day 3. The concentration of each marker continued to increase, to reach plateau concentration for lactose, citrate and glucose on days 3, 4, and 6, respectively.

Figure- 35 concentration of milk biochemical markers postpartum

Changes in the concentration of lactose, citrate, and glucose from birth until 7 days postpartum for non-diabetic mothers. Histograms are mean values with standard errors represented by vertical bar. (From Arthur et al. 1989).

Arthur and colleagues argued that to assess the usefulness of these biochemical markers of lactogenesis II, it was necessary to examine how the changes in concentration relate to milk yield. The first significant increase in lactose and citrate occurs between 24 and 48 hours after birth, the period during which lactogenesis II occurs, as judged from changes in milk yield.

Figure-36 daily milk yield

Comparison of the progressive changes in the milk yield (g/24 h) measured by test weighing the infant (shaded bars) to the breast-expression values of Roderuck et al. (white bars). Histograms are mean values with standard errors represented by vertical bars. (From Arthur et al. 1989)

The association between the volume of milk produced during a 24- hour period and the average concentration of the biochemical markers measured is further evidence suggesting that the changes in the their concentration are related to lactogenesis II

(Arthur et al. 1989). Arthur et al recommended using lactose and citrate as sensitive markers of lactogenesis II in humans rather than glucose, which shows erratic increase in concentration.

Figure- 37 the relationship between biochemical markers and daily milk production

The relationship between the average concentrations of lactose, citrate and glucose in milk during a 24 hour period and the volume of milk produced during that period.
(From Arthur et al. 1989)

It is postulated that 110 mM for lactose and 1 mM for citrate are the predetermined concentrations as markers of lactogenesis II. Lactose is the most osmotically active component of human milk and its synthesis is responsible for water being drawn into milk (Linzell & Peaker 1971). Therefore, a close relationship would be expected between the volume of milk produced and lactose synthesis. On the other hand, changes in the concentration of citrate in milk may result from changes in the rate of fatty acid synthesis (Faulkner & Peaker 1982), and so are not directly linked to changes in the volume of milk produced.

1.10.3 Measurement of the oral vacuum pressure and ultrasound imaging

Suckling on the mammary gland to obtain milk for nourishment is behaviour unique to mammals. Besides nourishment, suckling causes numerous responses in both the mother and infant, which are thought to have evolved to promote survival of the infant in harsh environmental conditions (Winberg 2005). Two theories exist to explain the milk flow from the mammary glands to the infant's oesophagus during suckling. The *first* claims that the peristaltic action of the tongue and pharynx is responsible for the transfer of milk from the mother to her infant (Cooper 1840; Ardan et al. 1958; Woolridge 1986). This theory presupposes the existence of lactiferous sinuses, but as these are not present in the human breast (Ramsay et al. 2005), this theory must be re-examined. The *second* theory claims that the negative vacuum (i.e. pressure) created by the downward and backward movement of the tongue is the main factor in the removal of milk from the mammary gland by the suckling infant (Waller 1936). Old studies have been inhibitive because of the large size of equipment used and the negative impact on the normal physiological process of mother-infant coupling during breastfeeding (Geddes et al. 2007).

Geddes et al at the University of Western Australia have published their work on the assessment of the oral vacuum in the novel setting of imaging the feeding process using a small ultrasound probe (Geddes et al. 2007). In their study the measured manometric negative pressure generated by the infant's tongue was correlated with the volume of milk removed, under ultrasound imaging.

The mean intraoral pressure was -114 ± 50 mmHg. The peak was -145 ± 58 mmHg and baseline was -64 ± 45 mmHg. Milk intake was not related to the peak or baseline pressures or the duration of the breastfeed.

Figure-38 Measurement of intraoral pressures during breastfeeding

A typical infant intra-oral pressure trace during a breastfeed. Peak vacuum (mean minimum pressure) ranges from -110 to -170 mmHg. Baseline pressure (mean maximum pressure) ranges from -50 to -60 mmHg (From Geddes et al. 2007)

With the synchronisation of ultrasound imaging of the infant's oral structures and the measurement of pressure applied by the infant to the breast, this study found that when the infant lowered its tongue the intra-oral negative pressure increased. Peak pressure coincided with the tongue in its lowermost position and subsequently as the infant lifted its tongue this decreased and milk flow ceased. It appears that milk only flows into the infant oral cavity when the downward movement of the posterior tongue creates a negative intra-oral pressure, highlighting the importance of this factor in milk removal, rather than the stripping action of the tongue (Geddes et al. 2007).

Figure-39 Ultrasonic images of the infants tongue during breastfeeding

The changes in infant tongue position during one suck cycle. (From Geddes et al. 2007)

1.11 Pethidine in Breast Milk and its effects on Breastfeeding:

Pethidine excretion in breast milk was studied in the early 1980s. Pieker et al studied 9 mothers who were 3 to 7 days postpartum and had received a single 50 mg intramuscular dose of pethidine. The highest measured breast milk concentration was 130 mcg/ L and it occurred 2 hours after the dose (Pieker et al. 1980). Based on estimation using the peak pethidine milk level from this study, an exclusively breastfed infant would receive about 20 mcg/kg of pethidine daily. Norpethidine was not measured in the study.

Two breastfeeding mothers who were 8 to 72 hours postpartum and receiving about 500 mg daily of IV pethidine had their milk sampled 2 to 4 times over 48 to 72 hours. Relationships between dose timing and milk sampling were not stated. The reported range of measured pethidine milk concentrations were 165-311 mcg/L. Norpethidine was undetectable in the milk (< 1.6 mcg/L) during the first 12 hours postpartum in one

patient and reached only 66 mcg/L during the same period in the other patient. In the 36 to 72 hour postpartum period, the reported range of norpethidine was 151- 333 mcg/L (Quinn et al. 1986). Using the peak pethidine milk concentration from this study, an exclusively breastfed infant would receive about 50 mcg/kg daily of pethidine from a maternal IV regimen of 500 mg per day, equal to about 6% of the maternal weight-adjusted dosage. Using the peak norpethidine milk concentration from this study, an exclusively breastfed infant would receive an additional 50 mcg/kg daily of norpethidine.

Five mothers who had undergone CS at term were given IV pethidine 75 mg after umbilical cord clamping and then 12.5 mg every 6 minutes via IV PCA as needed, for 20 to 48 hours postpartum (Wittels et al. 1990). When PCA pethidine was discontinued, oral pethidine 50 to 300 mg every 2 to 3 hours as needed was provided. Colostrum and milk were sampled from each of the mothers 6 times over 96 hours, beginning at 12 hours postpartum. Each mother's individual milk concentration and pethidine dose were not reported. Two mothers were able to provide enough milk in the 12 to 24 hour postpartum period, 3 were able in the 36 to 48 hour period and 4 were able in the 72 to 96 hour period. The average peak pethidine milk concentration was about 1100 mcg/L at 12 hours then 450, 250, 200, 150, 100 mcg/L at 24, 36, 48, 72 and 96 hours postpartum, respectively. Milk concentrations declined despite the daily dose of IV pethidine in the first 36 hours postpartum remaining nearly the same. The average individual cumulative intravenous pethidine dose in the first 12 hours postpartum, when the peak milk concentration was observed, was about 350 mg. The cumulative dose in the first 36 hours, mostly intravenous pethidine, was about 850 mg. The average cumulative oral pethidine dose over the 48 to 96 hour period was about 300 mg. The average cumulative IV plus oral pethidine dose over the entire 96 hours was about 1,300 mg (Wittels et al. 1990). Using this data, an exclusively breastfed infant would receive 165 mcg/kg daily of pethidine. During the first 36 hours postpartum period when intravenous dosing predominated and was approximately 25 mg per hour, an exclusively breastfed infant would receive about 56 mcg/kg daily, equal to 0.6% of the maternal weight-adjusted dosage. Using all the average milk levels reported over 96 hours postpartum, an exclusively breastfed infant would receive about 36 mcg/kg daily, also equal to 0.6% of the maternal weight-adjusted dosage (Wittels et al. 1980).

However, norpethidine was not measured in the study.

Eight breastfeeding women who were 1 month to 1 year postpartum and undergoing gynaecological surgery had their milk sampled 3 times after a single intraoperative dose of IV pethidine. Seven of the women received a 25 mg dose. Individual pethidine milk concentrations were not reported. Their average pethidine milk concentration was 176 mcg/L at 1 to 3 hours after the dose (range 134 to 244 mcg/L in 5 women 1 to 2 hours after the dose and 76 to 318 mcg/L in 3 women 2 to 3 hours after the dose). Only 3 of the women had detectable (>20 mcg/L) concentrations 8 to 10 hours after the dose (range 76 to 318 mcg/L). One woman received 75 mg pethidine. Her concentrations were 571 mcg/L 4 hours after the dose and 224 mcg/L 8 hours after the dose. None had detectable levels (>20 mcg/L) 24 to 28 hours after their dose. The authors determined that infants in this study received 1.2 to 3.5% of the maternal weight-adjusted dosage (Freeborn et al. 1980).

Infant Level: Six breastfed and 6 bottle-fed newborns had pethidine saliva concentrations measured at 2 to 3 hours of age, before their first feed, then again at 24 and 48 hours of age, on both occasions 1.5 hours after a feed. Their mothers had received a single dose of 100 mg IM pethidine 3 to 4 hours prior to delivery. Pethidine saliva concentrations in the breastfed newborns were higher at 24 hours of age than at 2 to 3 hours of age. They then decreased slightly by 48 hours of age but remained higher than at 2 to 3 hours of age. In contrast, pethidine saliva concentrations in the newborns that were bottle-fed decreased over the first 48 hours postpartum. Pethidine was eliminated from saliva very slowly by both groups of newborns. The authors surmised that the higher saliva pethidine concentrations in the breastfed newborns were due to oral absorption of pethidine from breastmilk (Freeborn et al. 1980).

Effects in Breastfed Infants:

In two controlled studies, repeated maternal pethidine doses after CS, including IV PCA pethidine, caused diminished alertness and orientation in 3- to 4-day old breastfed infants, compared to infants exposed to equivalent doses of morphine (Wittels et al. 1980; Wittels et al. 1997).

Possible Effects on Lactation:

Pethidine can increase serum prolactin (Onur et al. 1989). However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed. More importantly, pethidine is likely to interfere with infant nursing behaviour when given during labour (Nissen et al. 1995; Nissen et al. 1997; Rajan 1994).

The effects of pethidine on the breastfed neonate after CS have been inadequately explored and the potential adverse effects on lactogenesis and breastfeeding rates are unknown.

Chapter Two: Epidural Pethidine Post Caesarean Delivery: Maternal and Neonatal Drug Concentrations

2.1 Introduction

Over the last two decades the number of caesarean deliveries being performed globally has increased (Villar J et al. 2006). Although spontaneous vaginal birth still predominates in Australia, the incidence of caesarean delivery has risen from 18% of births in 1991 to 29 % in 2004 (Australian Social Trends, 2007). Pethidine is a μ -opioid receptor agonist with potent spinal and supraspinal effects (Ngan Kee 1998). Its moderately lipophilicity makes it attractive to use via the epidural route, where it shows a rapid onset of analgesia and a very low risk of respiratory depression. After i.v. administration in adults, the elimination half-life ($t_{1/2}$) is 3.3 ± 1.4 h (mean $\pm$ SD), volume of distribution (β) of 4.3 ± 1.7 L/kg and clearance (CL) of 12 ± 3 mL/min/kg (Tamsen A et al. 1982). It is liver metabolised to pharmacologically active norpethidine which is then renally excreted with a $t_{1/2}$ of 15-40 h (Armstrong PJ& Bersten A 1986).

Norpethidine may accumulate after prolonged or high dose pethidine administration or in renal failure (Szeto H et al. 1977) and cause adverse central nervous system effects such as agitation, tremulousness, hallucinations and convulsions (Armstrong PJ& Bersten A 1986; Kaiko R et al. 1972). Metabolic disposition of pethidine is impaired in the neonate (Caldwell J& Notarianni L 1978) and after i.v. administration to neonates and infants it has a median (range) $t_{1/2}$ of 10.7 (3.3-59.4) h, a steady-state volume of distribution of 7.2 (3.3-11) L/kg and a CL of 8 (1.8-34.9) mL/min/kg Pokela M et al. 1992). A mean (range) $t_{1/2}$ of 22.7(12-39) h for pethidine has also been reported in neonates whose mothers received pethidine during labour (Caldwell J et al. 1978)

Pethidine continues to be widely used in birth suites in Australasia and the United Kingdom, for labour analgesia via the i.m. route. The potentially harmful effects of parenteral pethidine in neonates were demonstrated approximately three decades ago (Shnider SM & Moya F 1964; Kuhnert B et al. 1979; Belfrage P et al. 1981; Hodgkinson R et al. 1978; Belsey E et al. 1981; Kuhnert B et al. 1985; Nissen E et al. 1997).

Breastfed infants of mothers who receive repeated post-caesarean doses of pethidine show diminished alertness on day 3 to 4 of life (Wittels B et al. 1990& Wittels B et al. 1997). Pethidine excretion in breastmilk following IM or IV administration post partum

has been investigated previously (Peiker G et al. 1980; Freeborn S et al. 1980; Quinn P et al. 1986) and infant exposure to pethidine (relative infant dose) ranged from 0.6-6% of the weight-adjusted maternal dose. Only one study measured norpethidine in milk, with the metabolite contributing an additional estimated infant dose of 6% (Freeborn S et al. 1986).

Administration of pethidine early after caesarean delivery using patient-controlled epidural analgesia (PCEA) is efficacious but there are significant plasma concentrations of pethidine and norpethidine in maternal plasma at the time therapy is ceased (Paech MJ et al. 1994). Given that lactation commences at around the same time, the primary aim of our study was to estimate infant exposure to both pethidine and norpethidine via breastmilk following PCEA administration of pethidine to women post caesarean section (CS). In addition, we aimed to measure pethidine and norpethidine in the exposed infant's plasma as a novel secondary measure of drug exposure via milk.

2.1.1 Aims and Objectives

- 1- To quantify maternal plasma and milk concentrations of pethidine and norpethidine after the use of pethidine PCEA after elective CS.
- 2- To quantify neonatal plasma concentrations and exposure to pethidine via breast milk.
- 3-To provide clinicians with adequate information to assist discussion of the risks and benefits of pethidine PCEA after CS, in relation to infant drug exposure.

2.2 Methods

This prospective observational study was approved by the Human Research and Ethics Committee of King Edward Memorial Hospital for Women and registered with the Australian and New Zealand Clinical trials registry. Twenty healthy women undergoing elective CS were recruited at antenatal clinics and gave written informed consent to their own and their infants' participation. All women were American Society of Anaesthesiologists (ASA) physical status classification I or II, scheduled for an elective CS at 37 or more weeks gestation, had no medical or obstetrical complications and planned to breastfeed. They were of mixed parity and breastfeeding experience. All had

consented to have combined spinal-epidural anaesthesia and pethidine PCEA for post-operative analgesia.

2.2.1 Study design

This study was designed as an observational study among women having elective CS and who were willing to breastfeed.

2.2.2 Study endpoints:

1. Plasma concentrations of pethidine and norpethidine at, and 6 hours after, cessation of PCEA postoperatively among breast feeding mothers or at 48 hours postoperatively if still on PCEA (3ml of heparinised blood in a non-gel tube).

2. Milk concentrations of pethidine and norpethidine at, and 6 hours after, cessation of PCEA postoperatively among breast feeding mothers or at 48 hours postoperatively if still on PCEA (2-3 ml milk in a 10ml yellow top tube polypropylene tapered tube).

The timing of maternal samples was given serious consideration in designing this study. This took into account the half-lives of pethidine and norpethidine and previous reports of norpethidine's increase in concentration after cessation of PCA. Maternal samples were aimed to best characterise the likely pharmacokinetic profiles. The use of PCEA pethidine for post CS analgesia in my institution is generally for 36-48 hours.

3. Plasma concentrations of pethidine and norpethidine 48 hours postoperatively among breast-fed infants exposed to maternal pethidine

4. Neurobehavioral scores (neonatal adaptive capacity score or NACS) of neonates at 48-72 hours of life.

2.2.3 Study participants

2.2.3.1 Inclusion criteria

1. ASA I and II

2. 18 years and over

3. Elective CS at term (37 weeks of gestation or more) and preference for pethidine PCEA for postoperative analgesia

4. Planning to breastfeed

2.2.3.2 Exclusion criteria

1. Non-elective CS

2. Preoperative opioid use

3. Multiple pregnancies

4. Maternal diabetes or impairment of glucose regulation

5. Abnormal renal function or severe pre-eclampsia

6. Intolerance or allergy to pethidine

7. Change to alternative analgesia to pethidine PCEA within 24 hours postoperatively

8. Inability to provide adequate breast milk samples

9. Neonates requiring admission to intensive care

10. Women over 40 years of age

2.2.3.3 Study design and sample size considerations

There are no published investigations in a similar study group; hence a sample size could not be derived from the literature. Convenience samples were chosen to look for possible effects of epidural pethidine on lactation and neonatal behaviours. The data obtained about epidural pethidine should allow future research into a number of areas under controlled conditions. For example, one might compare its neonatal effects or breast milk production with other postoperative analgesic methods (intravenous morphine; intrathecal morphine; oral oxycodone); or with other epidural opioids (morphine, fentanyl). It is not possible to estimate power for such studies at this time. A sample size of 20 patients was considered adequate for pharmacological analysis of

drug levels in breast milk samples, based on previous literature and the extensive experience of E/Professor K Ilett.

2.2.4 Ethical Issues

The design and methodology of this study took into consideration all the relevant recommendations by national and international bodies; of direct relevance are the Helsinki Declaration of the World Medical Associations and the updated statement of the National Health and Medical Research Council of Australia (NHMRC) in 2009.

The justification for this study is demonstrated by using appropriate methods for achieving its aims. This project was supervised by Professor Paech, who is an international authority in this field of research. All the resources and facilities were available to our research group either directly on site, or via our collaborative researchers. The merit of this research is that it evaluates a popular method of analgesia and serves the objective of providing valuable information which should be of interest to lactating women who deliver by CS.

Justice to all participants has been the priority of our research team. Any women experiencing problems with breast feeding after leaving the hospital are referred to the relevant hospital or community lactation services. Proper advice to all participants regarding feeding patterns was given during the research team visits. The results of this study will be made public via the hospital body for governing clinical research and the relevant media when appropriate. We are unaware of any potential burden this research may cause to any group.

Respect of patients' privacy and autonomy in decision making has been maintained; respect of all cultural values was adhered to strictly during the study. As this experiment used human tissue samples (blood and milk), only those samples collected to carry out the tests outlined in our protocol are to be used and there is no intention of dealing with these samples in any way that violates the consenting process or the NHMRC guidelines. We acknowledge though that samples need to be stored in our laboratory to perform the analyses in batches.

Non-Maleficence is clearly demonstrated in this study when considering performing an invasive blood test on the neonate. Although this may be uncomfortable to the baby and hurtful to the mother's feelings, we have taken all measures to make it less unpleasant.

Our experienced midwifery and research staff practiced a sensitive and professional approach to this matter. Moreover, we have limited the neonatal blood samples to one; this arose from a serious consideration of the need for frequent sampling against the potential harm to the newborn babies and their mothers. This consideration had led us to accept a one sample requirement in accordance with the ‘beneficence’ concept raised by the NHMRC Australia. This vital aspect of the ethical considerations for our study is clearly addressed in the written patient information sheet for the study group; it asked mothers to give consent for one blood sample to be taken from their babies approximately 48 hours after CS.

This study was approved by the Scientific and Ethics Committee for Human Research at King Edward Memorial Hospital for Women.

2.2.5 Study Assessments/ Measurements

Baseline:

- Age
- ASA status
- Weight and height / Body Mass Index (BMI)
- Parity
- Previous breast feeding experience and its duration
- Neonatal birth weight (g)
- Time of first feed (minutes, hours after delivery)

Postoperative:

- Duration and dose of pethidine PCEA and duration from last pethidine dose to neonatal blood collection.
- Blood and milk sampling as per primary endpoints above

- Venous samples collected into lithium heparin tubes, centrifuged and stored at – 21 degrees C before later assay using high performance liquid chromatography. Neonatal samples require 15 micro litres of the blood.
- Neonatal NACS scores (0-40) at 48-72 hours of life.

2.2.5.1 Measurement of Neonatal Neurologic Adaptive and Capacity Score

(NACS): The NACS was first described in 1982 (Amiel-Tison C et al. 1982) as a means of evaluating the neurobehaviour of term, healthy newborns and specifically to detect central nervous system depression from drugs administered to the mother during labour and delivery and to differentiate these effects from those associated with perinatal asphyxia. It is a recognised tool for obstetric analgesia research (Brockhurst NJ et al. 2000). The NACS items are organised into two scales: adaptive capacity and neurologic assessment. The latter is further divided into four subscales: passive tone, active tone, primary reflexes, and a general neurologic status assessment. Items are scored 0 (absent or grossly abnormal), 1 (mediocre or slightly abnormal), or 2 (normal), for a maximum score of 40. A score of 35 was arbitrarily deemed to be normal (Amiel-Tison C et al. 1982) and this has been supported (Brockhurst NJ et al. 2000). NACS was measured shortly after the cessation of maternal PCEA. Neonates in our study were assessed by one of two research midwives who were fully trained and experienced in the use of NACS.

2.2.5.2 Drug administration: Pethidine HCl (Hospira Australia Pty Ltd, Melbourne; 100mg/2mL) was administered by a PCEA mechanical device (Go Medical, Subiaco, Western Australia). This device is routinely used in the study institution, is simple to use and refill and is disposable. Pethidine 5 mg/mL was available in a 4 mL bolus of 20 mg, with lockout interval of 20 minutes and no 4 hour limit (Banks S& Pavy T 2001) starting within a few hours of birth and continued for 24 – 48 hours postoperatively if required. Concurrent administration of non-opioid analgesic drugs was permitted and rescue analgesia, if required, was with tramadol.

2.2.5.3 Milk and plasma sampling: Maternal plasma and milk samples (1-2 mL each) for pethidine and norpethidine analysis were collected within 2 h of drug cessation and also if possible six hours later, or at 48 h and 6 h later if pethidine was used until 48 hours. Neonatal capillary blood samples (0.5mL) were collected for drug assay at the time the Guthrie test was performed, usually around 48-72 hours after birth. The latter sample was timed to be shortly after the cessation of maternal PCEA and as close as possible to one of the maternal blood samples. Date and time of each sample was recorded and samples were referenced to the date and time of birth for the subsequent data analysis.

2.2.5.4 Pethidine and norpethidine measurement by liquid chromatography-tandem mass spectrometry (LC/MS): Pethidine and norpethidine were extracted from 20µL of milk or plasma by protein precipitation with 1mL of methanol containing d₄-pethidine and d₄-norpethidine as internal standard (Toronto Research Chemicals Inc, North York, ON, Canada; 2µg/L). An 8µL aliquot of the supernatant was injected onto the LC/MS system consisting of a Waters Acquity UPLC (Milford, MA, USA) coupled with a Waters Premier XE MS-MS (Milford, MA, USA). The LC mobile phases were (A) 25% acetonitrile in 10mM ammonium acetate/0.5% acetic acid, and (B) 50/50 methanol/acetonitrile. Elution of the analytes through a Waters ACQUITY UPLC BEH C₁₈ 2.1 x 100mm x 1.7 µm (Wexford, Ireland) was effected by gradient flow of 0.4mL/min 70% A and 30% B for 0.5min, then 90% B for 1.05 min followed by 0.35min reconditioning. In ESI⁺ mode, the MRM protonated adduct transitions m/z 248.2 to 174.1 and m/z 234.2 to 160.0 for pethidine and norpethidine respectively, and m/z 252.2 to 224.2 and m/z 238.2 to 164.0 for d₄-pethidine and d₄-norpethidine respectively were monitored. With capillary voltage 0.6kV, cone voltage 18V, collision energy 11.0eV, source temperature 400°C, the retention time for pethidine and norpethidine and their labelled internal standards were 1.14 and 1.13min respectively. Linearity was established for both pethidine and norpethidine over the concentration range of 0.97 µg/L to 1944µ g/L ($r^2 = 0.998$) and 1.07µg/L to 2134 µg/L ($r^2 = 0.999$) respectively in plasma. Linearity was established for both pethidine and norpethidine over the concentration range of 0.97 µg/L to 93.5µ g/L ($r^2 = 0.997$) and 1.07 µg/L to 100.5 µg/L ($r^2 = 0.997$) respectively in milk. The relative standard deviations (RSDs)

for pethidine and norpethidine in milk at 1 µg/L were 5.7% and 11.6% respectively. The RSDs for pethidine and norpethidine in plasma at 0.2 µg/L were 5.2% and 18.5% respectively. These latter concentrations in milk and plasma respectively, were considered satisfactory as lower limits of quantitation (<20%) for both these compounds. Limits of detection for both compounds were set at 3-times baseline noise in individual samples (approximately 0.05 µg/L).

Matrix effects, absolute recovery and process efficiency for the LC/MS-MS method were investigated using 5 blank plasma and milk samples from different patients that were spiked with pethidine and norpethidine at 1 µg/L, 10µg/L and 100 µg/L and for the internal standards pethidine-d⁴ and norpethidine-d⁴ at 100 µg/L.

For pethidine in plasma, matrix effects (mean±SD) were 86±15%, 90±5% and 89 ±2%, absolute recoveries were 100±20%, 104±6% and 97±3% and process efficiencies were 85±15%, 94±8% and 87±3% respectively. For norpethidine in plasma, matrix effects were 83±15%, 83±6% and 82 ±2%, absolute recoveries were 105±11%, 108±3% and 98±2% and process efficacies were 86±10%, 90±8% and 81±3% respectively. Inter-patient RSD's at the same three concentrations were 6.1%, 5.8% and 2.1% for pethidine and 5.9%, 6.2% and 2.9% for norpethidine respectively. Matrix effects, absolute recoveries and process efficiencies for the internal standards were 92±2%, 100±2% and 92±4% respectively for pethidine-d⁴ and 86±2%, 101±2% and 88±3% respectively for norpethidine-d⁴.

For pethidine in milk matrix effects (mean±SD) were 76±9%, 80±6% and 79 ±1%, absolute recoveries were 107±17%, 88±9% and 96±2% and process efficiencies were 82±13%, 70±9% and 77±2% respectively. For norpethidine in milk, matrix effects were 87±20%, 83±3% and 76 ±1%, absolute recoveries were 93±20%, 87±5% and 96±3% and process efficacies were 78±10%, 73±4% and 72±2% respectively. Inter-patient RSD's at the same three concentrations were 10.3%, 10.2% and 2.8% for pethidine and 12.5%, 4.8% and 3.8% for norpethidine respectively. Matrix effects, absolute recoveries and process efficiencies for the internal standards were 82±2%, 100±4% and 81±2% respectively for pethidine-d⁴ and 74±1%, 75±2% and 101±4% respectively for norpethidine-d⁴.

2.2.6 Data analysis: Absolute infant dose (AID; sometimes called theoretic infant dose) was calculated as the product of drug concentration in milk (µg/L) and daily milk

volume ingested by the infant (L/day) (Bennett P 1996). Daily milk volumes for each infant, at each feeding time, were estimated as outlined (Jansson L et al. 2007), using individual infant age in hours to interpolate milk volume from a previously published mean production-time plot (Jansson L et al. 2007). Our Sigma Plot II software was used to accurately extrapolate the relevant daily milk volume by age to the hour to minimise miscalculations.

Figure- 40 (daily milk volume in relation to age of the newborn in days since birth)

Relative infant dose (RID) of pethidine was estimated from the AID expressed as a percentage of the weight-adjusted maternal dose of pethidine (Neville M et al. 1988) RID for norpethidine was derived similarly after the AID was expressed in pethidine equivalents by multiplying by the pethidine: norpethidine molecular weight ratio (247.332/233.306). In this way the RID for norpethidine can be directly related to the pethidine dose, and both pethidine and its metabolite can be summed to give a total RID estimate as pethidine equivalents. Infant exposure to pethidine and norpethidine from milk was calculated as the concentration of each drug in the infant's plasma as a percentage of that in mother's plasma at the same time. Data have been summarised as mean and 95% confidence interval (CI), or median and inter-quartile range (IQR), or median and range as appropriate. Statistical significance between groups was assessed by Student's t-test on $\log_{10}$ transformed data using SigmaStat Version 3.5 (Systat Software Inc. Chicago, IL, USA).

2.3 Results

The first woman in the study was transferred to another hospital in Perth for her ongoing care; therefore she contributed to the first samples of her plasma and milk and to her neonate's plasma. We included her results in the analysis as she did not withdraw her consent to participate in the study. Maternal (age, weight and parity) and neonatal (time to first breastfeed, weight) demographics are shown in Table 9.

Table-9 Demographic descriptors for the mothers and their infants (study group)

Patient Number	Age (years)	Weight (kg)	Parity	Time to first breastfeed (min)	Neonatal Birth Weight (kg)
1	37	76	1	52	3.355
2	28	86	1	11	3.575
3	23	81	2	52	3.415

4	30	70	2	116	3.405
5	39	70	4	37	3.68
6	24	96	2	171	3.645
7	30	97	3	82	2.885
8	26	117	1	105	2.76
9	38	140	2	59	4.07
10	32	80	3	92	3.3
11	35	113	1	120	4.06
12	40	73	2	268	3.634
13	27	99	2	155	3.585
14	34	92	2	79	3.99
15	29	71	2	180	3.665
16	31	97	3	52	3.425
17	32	61	3	80	3.33
18	29	85	1	112	3.235
19	37	84	3	145	3.34
20	36	62	1	10	3.44
<hr/>					
Mean	32	87	2	87	3.49
<hr/>					
(95%C					

I)	(30-34)	(79-96)	(1-4) ^a	(52-126) ^b	(3.34-3.64)
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Data are mean (95% CI) unless otherwise specified; ^a median (range); ^b median (IQR)

The neonates comprised 9 males and 11 females. Characteristics of the maternal pethidine dose, its relation to the neonatal blood sampling and NACS administration, as well as the NACS, are shown in Table 10.

Table-10 Maternal pethidine dose data, times infant blood sampling and NACS testing and NACS result

Patient number	Total pethidine dose (mg)	PCEA duration (h)	Pethidine (mg/h)	Weight adjusted maternal dose (µg/kg/d)	Time last pethidine dose to baby blood sample (min)	Time last pethidine to NACS (min)
1	840	48	17.5	5526	60	45
2	750	50.5	14.85	4144	0	0
3	180	49	3.7	1096	0	0
4	375	22	17	5829	230	230
5	895	54	16.6	5691	10	5

6	355	30.5	11.6	2900	780	780
7	765	50	15.3	3786	-25	60
8	810	23	35.2	7221	150	150
9	190	39.5	6.2	1063	1200	1200
10	800	51	16	4800	120	120
11	430	47	9.15	1943	35	30
12	900	39	23	7562	0	0
13	1100	43	25.6	6206	330	230
14	245	17	14.4	3757	285	242
15	315	48	6.6	2231	350	350
16	590	48	12.3	3043	45	50

17	760	48.5	15.7	6177	15	10
18	320	13	24.6	6946	420	600
19	400	44	9.1	2600	240	360
20	1050	45	23.3	9019	90	90
Median	670	41 (35-	15.9	4577	105	105 (25-269)
(IQR)	(346-818)	46) ^a	(12.5-19.2) ^a	(3583-5571) ^a	(14-295)	

Data are median (IQR) unless otherwise specified; ^a mean (95% CI).

Time from last pethidine administration til baby blood sample collection in patient number 7 is shown as (-25), to reflect that neonatal blood was collected 25 min before the last dose of pethidine administered by the mother.

The median (IQR) total pethidine dose of 670 (346-818) mg was delivered at a mean (95%CI) rate of 15.9 (12.5-19.2) mg/h over a median of 41 (35-46) h. The maternal weight-adjusted pethidine daily dose (4577 (3383-5571) µg/kg/d; mean (95%CI)) was calculated as 24 times the PCEA delivery rate, divided by body weight. The neonatal blood sampling for drug analysis and the NACS testing were done at the same median time of 105 min after cessation of maternal pethidine. The mean (95%CI) NACS score for the neonates was 33.6 (32.2-34.9), with a range from 28 to 38.

For logistic reasons, not all 20 scheduled milk samples were able to be collected for each sampling period. For sampling periods 1 and 2, only 12 and 14 samples respectively were available for drug assay. Table 11 summarises the timing since birth of maternal blood, milk and neonatal plasma samples in hours.

Table 11: Time in hours since birth of maternal and neonatal samples collected

age M1 hrs	age M2 hrs	age at MB1 hrs	age at MB2 hrs	age at BB hrs
46	ND	46	ND	49
49.5	57	49	57	49.5
48	55	48	ND	48
25.5	30	25.5	ND	28
48.5	ND	48	ND	48
ND	43	ND	43	44
47	ND	47	55.5	49
25	30	25	30	25
ND	ND	ND	ND	50
50.5	58.5	50.5	58.5	50
49	56	49	56	49
ND	44.5	ND	45	ND
ND	47.5	ND	47.5	48
ND	ND	ND	25	24.5
ND	48.5	ND	48.5	48.5
48	ND	48	ND	48
48	55	48	55.5	48
ND	20	ND	20	20
48.5	51	48.5	50	48.5
47	53	47	53	48

All sampling times refer to time in hours since birth of the infant. M1=maternal milk sample 1, M2= maternal milk sample 2, MB1= maternal milk sample 1, MB2= maternal milk sample 2 and BB= baby blood sampling time.

Table 12 summarises the plasma concentrations of pethidine and norpethidine in mothers and their neonates, as well as the estimated absolute and relative infant dose data for both drugs. Between the first and second sampling times, mean plasma concentrations of pethidine decreased by 65% while those of norpethidine decreased by only 38% (Table 11).

Table-12 Pethidine and norpethidine in maternal milk and plasma, and calculated neonatal (“infant”) dose and exposure to pethidine and norpethidine via milk

Parameter	Pethidine	Norpethidine
<i>Maternal</i>		
Milk sample 1 ^a (µg/L)	421 (303-529); 12	414 (309-490); 12
Milk sample 2 ^a (µg/L)	176 (120-321); 14 ^f	373 (258-487); 14
Plasma sample 1 ^a (µg/L)	326 (249-403); 13	257 (193-251); 13
Plasma sample 2 ^a (µg/L)	114 (76-151); 15 ^g	160 (99-221); 15
<i>Neonate</i>		
Absolute infant dose 1 ^b (µg/kg/d)	20 (14-27); 12	21 (16-26); 12
Absolute infant dose 2 ^b (µg/kg/d)	10 (7-13); 14 ^h	22 (12-32); 14
Relative infant dose 1 (%) ^c	0.7 (0.1-1.4); 12	0.7 (0.3-1); 12 ^d
Relative infant dose 2 (%) ^c	0.3 (0.1-0.5); 14 ⁱ	0.6 (0.2-1); 14 ^d
Infant plasma (µg/L)	3.0 (0.0-6.1); 17	0.6 (0.2-1.0); 17
Infant Exposure (%) ^e	1.4 (0.2-2.8); 17	0.4 (0.2-0.6); 17

Data are mean (95% CI); N. ^a two samples collected either within 2 h of PCEA cessation and also if possible six hours later, or at 48 hours and 6 h later if pethidine was used until 48 hours; and denoted samples 1 and 2 respectively. ^b absolute infant dose for samples 1 and 2 respectively. ^c relative infant dose for samples 1 and 2 respectively. ^d expressed as pethidine equivalents (see Methods). ^e concentration in infant plasma as percentage of that in maternal plasma. ^f $P < 0.001$ compared with milk sample 1. ^g $P < 0.001$ compared with plasma sample 1. ^h $P < 0.01$ compared with absolute infant dose for sample 1; ⁱ $P < 0.05$ compared with relative infant dose for sample 1.

Mean (95%CI) milk volumes at the first and second sampling times were 172 (140-204) mL/d and 195 (153-237) mL/d, respectively. Both AID and RID were similar for both pethidine and norpethidine for the first milk sampling period and for norpethidine at the second sampling period. By contrast AID and RID for pethidine were approximately halved in the second milk sampling period, in line with the concentration data (Figure 41). Figure 41 shows a scatter plot of pethidine and norpethidine concentrations in milk versus time of sampling expressed as infant age (h). These data show that pethidine in milk decreased over time (($t = 4.18$, $P < 0.001$, 95% CI for difference of means= 0.200 to 0.590) in the 6 hours between the first and second sampling times, whereas norpethidine remained in a similar range across time.

Figure-41 Scatter plot of pethidine (closed circles) and norpethidine (open circles) concentrations in milk.

Logistic regression was performed on data from the 26 samples of milk to verify that the scatter of pethidine milk concentration was not significantly different. (Adjusted $R^2 = 0.056$, coefficient = -0.0077, t-test value = -1.563 and p-value = 0.131). This proved that the slope of the curve was not significantly different from zero. Combining pethidine and norpethidine (as pethidine equivalents) gave RID's of 1.4% at the first milk sampling period and 0.9% for the second milk sampling period. Neonate plasma samples were not available for three subjects, while four results for pethidine and six for norpethidine were below the assay limit of detection and were reported as the approximate limit of detection (0.05 µg/L), so that a conservative estimate of infant exposure (plasma) relative to maternal exposure (plasma) could be calculated. The mean concentrations of pethidine and norpethidine in the neonate's plasma were 3 µg/L and 0.6 µg/L respectively. Reporting several infant plasma concentrations at the assay limit of detection increased the mean concentration of pethidine by 3.1% and that of norpethidine by 0.4%. In the mothers, mean concentrations of pethidine and norpethidine at the two sampling times were 236 and 114 µg/L and 257 and 160 µg/L respectively. The ratio of drug in the infant's plasma to that in mother's plasma was

informative, with an indicative exposure of 1.5% for pethidine and 0.4% for norpethidine.

2.4 Discussion

The combined pethidine plus norpethidine milk RID estimates of 1.4% and 0.9% at our two separate sampling times, compare favourably with the notional 10% cut-off value of acceptability that has been applied to a wide range of drugs (Bennett P 1996) , provided the drug effects in the infant are also acceptable (Neville MC& Walsh C 1996)). Our RID values are similar to the 1.3% that can be calculated using the highest pethidine concentration occurring after a 50 mg i.v.dose (Peiker G et al. 1980) and lower than the 1.2-3.5% after 25-75 mg single i.v. pethidine doses (Freeborn S et al. 1980), or the 6% for pethidine plus an additional 6% for norpethidine after 500 mg i.v. pethidine daily (Quinn Pet al. 1986). Note however, that only our own study and that by Quinn et al measured both pethidine and norpethidine in milk. The therapeutic dose of pethidine in neonates varies from 0.625 mg/kg (Purcell-Jones G et al. 1987) up to 1-1.5 mg/kg (Siberry GK, Iannone R 1997; Yaster M, Deshpande JK 1988; Miall-Allen VM, Whitelaw AG 1987) and may be administered 3-4hourly if required (Siberry GK& Iannone R 1997). If we sum the mean AIDs of 20 and 10 µg/kg/d for pethidine and 21 and 22 µg/kg/d for norpethidine, and average across the two observation times, the combined dose is approximately 18 µg/kg/d. Compared with a single neonatal recommended therapeutic dose of 1000 µg/kg, this represents 1.8% exposure via milk.

Our RID estimates are also supported by our novel neonatal: maternal plasma exposure of 1.4% for pethidine and 0.4% for norpethidine. However, we recognise that these latter data are derived from a ratio estimated at a single time and may not be as robust as those from the milk RID which come from multiple samples over a 6 hour time period. Interestingly, the mean ratio of pethidine: norpethidine in neonatal plasma (3.75) was higher than the mean ratio in the ingested milk (2.23), which is consistent with earlier observations (Pokela M et al. 1992; Caldwell J et al. 1978) that neonatal disposition of norpethidine is slower than that of pethidine.

The plasma concentrations of both pethidine and norpethidine for both neonates and their mothers in our study were well below the toxic levels of 2346 µg/L and 1856 µg/L for pethidine and norpethidine respectively for adults (Kaiko R et al. 1983; Geller R 1993). This study shows a trend towards a lower pethidine concentration in both

plasma and milk at the second sampling time compared to the first. This is a reflection of cessation of maternal use of pethidine. The mean plasma pethidine concentrations (326 µg/L and 114 µg/L at sampling times 1 and 2 respectively) found in this study were below the mean minimum effective analgesic concentration in plasma for severe post-operative pain (450 µg/L) after parenteral administration, except in patients 3 (531 µg/L), 5 (507 µg/L) and 17 (537 µg/L) at the first sampling time. This supports a primarily spinal cord analgesic action of epidural pethidine and is in accordance with other studies showing analgesic efficacy with significantly lower doses of pethidine administered via the epidural route (Paech M et al. 1994; Sjöström S et al. 1988).

The trend of maternal plasma norpethidine concentration followed a similar pattern to that of pethidine, with norpethidine concentrations at the second sampling time lower than those at the first occasion. Norpethidine milk concentrations remained higher than corresponding plasma concentrations, a similar relationship to that observed for the parent drug. This finding of lower plasma concentration at the later sampling time differs from a randomised cross-over trial of PCEA and patient-controlled intravenous pethidine in which plasma norpethidine continued to increase rise after 24 hours (Paech M et al. 1994). Differences in timing of sampling may explain the different results and the latter study did not measure milk or neonatal plasma concentrations. An alternative explanation is that our study subjects had better post-operative analgesia and needed less pethidine over the period of the study. Direct comparison with the study of Paech et al is of minimal value due to its cross-over design and short period of PCEA of only 12 hours.

Infants in our study did not show signs of excessive sedation or abnormal breastfeeding behaviour. The NACS are difficult to interpret, especially in the absence of controls, but confidence intervals overlapped with the arbitrary normal mean score of 35 (the normal range has never been determined) (Brockhurst et al. 2000). The NACS has been criticised because of poor test reliability (Halpern S et al. 2001). The neonates in our study were assessed by one of two research midwives who were fully trained and highly experienced in the use of the NACS instrument. Despite its significant limitations, the NACS is easy to perform at the bed side and, in the absence of suitable alternatives, has been used widely to demonstrate drug effects and differences between interventions in obstetric anaesthesia research (Brockhurst et al. 2000).

This study has several limitations. First, this type of observational study does not allow statistical estimation of sample size ‘a priori’, but the number of patients was based on previous experience of drug studies of this nature in lactating women and the advice of a very experienced investigator in this area of research, E/Professor Ilett. Studies of drug in milk (at steady-state) have traditionally involved (a) a collection of single observations of drug concentration in milk (and calculation of RID) in several individual cases or reports (often $n=5$), or (b) measurement of drug concentrations in milk from several individual patients with 5-6 samples collected over a dose interval and then calculation of RID ($n=8-10$). This latter design was not applicable because of the clinical setting with PCEA, which has attendant inter-patient variability in frequency of dosing and dose requirement. I therefore chose a “sparse sampling” study design with two samples being taken, essentially a modified design (a). This design was used by Ilett and coworkers recently in their study of tramadol in breast milk (Ilett et al. 2008). The first sample was collected at or about the cessation time for PCEA administration, and the second 6 hours later. The first sample could be considered to represent steady-state condition with regard to pethidine concentration. The timing of the second sample at 6 h later was decided on the basis that norpethidine, which has a long half-life might persist in milk after cessation of drug administration (Paech et al. 1994), while pethidine with a much shorter half-life might be expected to show decreasing milk concentration. With pethidine PCEA, a pragmatic approach that provided likely both adequate data and feasibility was to recruit 20 patients, although I acknowledge that more robust data may have been obtained with a larger sample size. The second limitation of the study was that milk: plasma ratios were not calculated as it was not possible to do so with our study design. In any case the milk: plasma ratio *per se* is not useful as an indicator of infant exposure or risk. Third, there was wide variability in the maternal consumption of pethidine. However, this reflects normal clinical practice and use of a patient-controlled analgesia device, whereby wide variability in opioid requirements exists and drug administration tends to be higher in the first 24 hours post-operatively, decreasing thereafter.

Not all planned milk samples were collected for logistic reasons, specifically when their timing fell at night or early hours of the morning, when our research team was not be available for collection and storage. This resulted in the collection of only 26 milk samples rather than 40. This may have impacted negatively on the precision of the data

presented, however; the lack of pharmacokinetic data regarding epidural pethidine use after CS still made it clinically useful to perform the assays and publish the results.

Timing of maternal samples for both mothers and babies was another significant factor to consider and created another issue. Timing was referenced to the hour of birth (time zero) and subsequently all timings were related to that preference. Maternal sample collection was relatively easy and most blood samples related well to the corresponding timing of milk samples. Timing the neonatal plasma test was difficult. An attempt was made to time all Guthrie tests conducted by the midwifery staff on the recruited infants to correspond with a time of maternal sampling. This was not an easy task and table 11 that some of the neonatal samples were collected at a time which did not correspond to any maternal sample. However, all neonatal samples were taken within a 6 hours period or slightly after the second maternal sample. This may have skewed the neonatal data and consequently AID and RID calculation to a small extent. A further limitation to the calculation of AID and RID is that the calculations rely on the estimated daily milk volume produced by mothers, as described in the 'Methods' section of chapter 2 of this thesis. This also adds uncertainty to the reliability of AID and RID estimation but is standard practice because there is no other feasible approach.

This study findings are only relevant to a limited population of patients globally; however, this population is not insignificant in Australia and New Zealand. The author acknowledges that other epidural opioids are used more frequently in other countries and that analgesia with subarachnoid opioids (morphine, sufentanil and fentanyl) is common practice both in the region and abroad.

2.5 Conclusions

In summary, this study shows that the mean RIDs for pethidine and norpethidine (average of the two observations) via milk were 0.5% and 0.65% respectively of the maternal weight-adjusted pethidine dose. Infant exposure measured as the ratio of drug in infant to maternal plasma was also low at 1.4% for pethidine and 0.4% for norpethidine. I conclude that maternal use of pethidine by PCEA for post CS analgesia appears unlikely to cause harm to the breastfeeding neonate. This study should assist with discussing the safety of pethidine PCEA for CS analgesia and provides the basis for future studies to be conducted, especially in Australia and Asia where this method of analgesia is most often used.

Appendix 1: Pethidine and norpethidine measurement by liquid chromatography-tandem mass spectrometry (LC/MS-MS)

Sample extraction and LC-MS/MS conditions:

Analytical reference standards of pethidine (1 mg/mL and norpethidine (100 µg/mL) purchased from Cerilliant Corporation, Round Rock, TX, USA were used in constructing standard curves for each analytical batch of plasma and milk samples. Pethidine and norpethidine were extracted from 20 µL of milk or plasma by protein precipitation with 1 mL of methanol containing d₄-pethidine and d₄-norpethidine as internal standard (Toronto Research Chemicals Inc, North York, ON, Canada; 2 µg/L). An 8 µL aliquot of the supernatant was injected onto the LC/MS-MS system consisting of a Waters Acquity UPLC (Milford, MA, USA) coupled with a Waters Premier XE MS-MS (Milford, MA, USA). The LC mobile phases were (A) 25% acetonitrile in 10 mM ammonium acetate/0.5% acetic acid, and (B) 50/50 methanol/acetonitrile. Elution of the analytes through a Waters ACQUITY UPLC BEH C₁₈ 2.1 x 100 mm x 1.7 µm (Wexford, Ireland) was effected by gradient flow of 0.4 mL/min 70% A and 30% B for 0.5 min, then 90% B for 1.05 min followed by 0.35 min reconditioning. In ESI⁺

mode, the MRM protonated adduct transitions m/z 248.2 to 174.1 and m/z 234.2 to 160.0 for pethidine and norpethidine respectively, and m/z 252.2 to 224.2 and m/z 238.2 to 164.0 for d_4 -pethidine and d_4 -norpethidine respectively were monitored. With capillary voltage 0.6kV, cone voltage 18V, collision energy 11.0eV, source temperature 400°C, the retention time for pethidine and norpethidine and their labelled internal standards were 1.14 and 1.13min respectively.

Method validation:

In plasma, linearity of the assay was established for both pethidine and norpethidine over the concentration range of 0.97 $\mu\text{g/L}$ to 1944 $\mu\text{g/L}$ ($r^2 = 0.998$) and 1.07 $\mu\text{g/L}$ to 2134 $\mu\text{g/L}$ ($r^2 = 0.999$) respectively. In milk, linearity was established for both pethidine and norpethidine over the concentration range of 0.97 $\mu\text{g/L}$ to 93.5 $\mu\text{g/L}$ ($r^2 = 0.997$) and 1.07 $\mu\text{g/L}$ to 100.5 $\mu\text{g/L}$ ($r^2 = 0.997$) respectively. Matrix effects, absolute recovery, process efficiency and inter-patient variability (relative standard deviations, RSD) were investigated using 5 blank plasma and milk samples from different patients that were spiked with pethidine and norpethidine at 1 $\mu\text{g/L}$, 10 $\mu\text{g/L}$ and 100 $\mu\text{g/L}$ and with the internal standards pethidine- d_4 and norpethidine- d_4 at 100 $\mu\text{g/L}$ (Sample Set 1). Spiked post-extraction addition extracts for the same 5 samples (Sample Set 2) were also prepared at concentrations equivalent to those described above by using a fixed volume of the extract obtained after the methanol-precipitation step. Finally, “pure solutions” of all analytes at concentrations equivalent to those described above were prepared by diluting with an aqueous/methanol solvent as per the typical extraction procedure (Sample Set 3). These data are summarised in Table A1 for plasma and Table A2 for milk. In a separate assessment, the RSDs for pethidine and norpethidine in plasma at 0.2 $\mu\text{g/L}$ were 5.2% and 18.5% respectively. These latter plasma concentrations were considered satisfactory as lower limits of quantitation (<20%) for both these compounds. Limits of detection for both compounds were set at 3-times baseline noise in individual samples (approximately 0.05 $\mu\text{g/L}$). For plasma, accuracy of the analytical procedure was assessed at 5, 10, 50, 200 and 1000 $\mu\text{g/L}$ for pethidine and 5, 10, 50 and 200 $\mu\text{g/L}$ for norpethidine ($n=5$ each). Mean accuracy ranged from 98-102% (SD range 1.3-3.7%) for pethidine and from 95-102% (SD range 2-6.8%) for norpethidine. For milk, accuracy of the analytical procedure was assessed at 5, 10, 50, 100, 200 and 500 $\mu\text{g/L}$ for both pethidine and norpethidine ($n=3-4$ each). Mean accuracy ranged from 97-

104% (SD range 1.6-8.1%) for pethidine and from 98-106% (SD range 0.5-11.2%) for norpethidine.

Table A1. Matrix effects, recovery, process efficiency and inter-patient variability of pethidine and norpethidine assay in plasma (data as mean±SD (range))

	Analyte			Internal Standard
	Pethidine			d ₄ -Pethidine
	1 µg/L	10 µg/L	100 µg/L	100 µg/L
Matrix effect (%) ^a	86±15(66-101)	90±5(83-99)	89±2(85-91)	92±2(88-95)
Absolute recovery (%) ^b	100±20(74-126)	104±6(95-113)	97±3(93-101)	100±2(97-104)
Process efficiency (%) ^c	85±15(64-101)	94±8(84-103)	87±3(81-90)	92±4(87-97)
Inter-patient RSD (%)	6.1	5.8	2.1	
	Norpethidine			d ₄ -Norpethidine
	1 µg/L	10 µg/L	100 µg/L	100 µg/L
Matrix effect (%) ^a	83±15(67-99)	83±6(75-89)	82±2(79-85)	86±2(82-90)
Absolute recovery (%) ^b	105±11(94-123)	108±3(103-111)	98±2(95-101)	101±2(98-105)

Process efficiency (%) ^c	86±10(76-101)	90±8(77-99)	81±3(75-85)	88±3(82-93)
Inter-patient RSD (%)	5.9	6.2	2.9	

Matrix effect=Response for Sample Set 2 x100/Response for Sample Set 3; ^b Absolute recovery= Response for Sample Set 1 x100/Response for Sample Set 2; ^c Process efficiency= Response for Sample Set 1 x100/Response for Sample Set 3

Table A2. Matrix effects, recovery, process efficiency and inter-patient variability of pethidine and norpethidine assay in milk (data as mean±SD (range))

	Analyte	Internal Standard		
	Pethidine			d ₄ -Pethidine
	1 µg/L	10 µg/L	100 µg/L	100 µg/L
Matrix effect (%) ^a	76±9(67-87)	80±6(77-91)	79±1(78-80)	82±2(79-84)
Absolute recovery (%) ^b	107±17(90-134)	88±9(72-94)	96±2(94-100)	100±4(94-105)
Process efficiency (%) ^c	82±13(65-97)	70±9(56-81)	77±2(75-79)	81±2(80-83)
Inter-patient RSD (%)	10.3	10.2	2.8	
	Norpethidine			d ₄ -Norpethidine
	1 µg/L	10 µg/L	100 µg/L	100 µg/L
Matrix effect (%) ^a	87±20(70-120)	83±3(81-89)	76±1(74-77)	74±1(72-75)
Absolute recovery (%) ^b	93±20(65-118)	87±5(81-93)	96±3(93-101)	75±2(72-78)
Process efficiency (%) ^c	78±10(68-91)	73±4(67-77)	72±2(70-74)	101±4(97-108)
Inter-patient RSD (%)	12.5	4.8	3.8	

^a Matrix effect=Response for Sample Set 2 x100/Response for Sample Set 3; ^b Absolute recovery= Response for Sample Set 1 x100/Response for Sample Set 2; ^c Process efficiency= Response for Sample Set 1 x100/Response for Sample Set

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