The FILL Trial (Fluid in Low Risk Labour)

The Effect of Conservative versus Usual Intrapartum Fluid Management for Low Risk Women with Epidural Analgesia on Newborn Weight Loss in Breastfed Infants

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Abstract

The Effect of Conservative Versus Usual Intrapartum Fluid Management for Women with Epidural Analgesia on Newborn Weight Loss in Breastfed Infants

The FILL Trial (Fluid in Low Risk Labour)

There is uncertainty regarding how much intravenous fluid should be given to women in the intrapartum period. There are no published protocols or guidelines available to address fluid management in labour to optimize care for women and their infants. The absence of an evidence-based approach to intrapartum fluid management may result in fluid overload, with consequent maternal and newborn morbidity. The FILL Trial sought to answer the question, for low risk women receiving epidural analgesia in labour, ‘what is the effect of a conservative protocol for fluid management versus usual care on breastfed newborns’ weight loss prior to hospital discharge?

The FILL Trial was a single site randomized controlled trial comparing a conservative protocol of fluid management with usual care for low risk women receiving epidural analgesia in labour. Women in the conservative care group received an IV volume prior to epidural analgesia initiation of < 500 ml and an IV infusion rate of 110 ml per hour. Women in the usual care group received an IV volume prior to epidural analgesia initiation of >500 ml and an IV infusion rate of 200 ml per hour. The primary outcome of interest was the proportion of breastfed infants who lost > 7% of their birth weight prior to discharge.
Two hundred women participated, 100 in the conservative care group and 100 in the usual care group. Forty-four infants in the conservative care group and 48 infants in the usual care group lost > 7% of their birth weight, $p=0.57$. There were no statistically significant differences between groups for breastfeeding outcomes or measures of newborn well being. More babies in the conservative care group required initial admission to the neonatal intensive care unit for septic work up for maternal fever. No septic work ups of the babies yielded positive results. More instrumental vaginal deliveries occurred in the conservative care group.

No change in current practice is warranted for intrapartum intravenous fluid volumes < 2500 ml. Future research should focus on the creation of more evidence regarding safe volumes of intravenous fluid during labour.
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Chapter One

Background and Problem Statement

Women seek the care of physicians, midwives and nurses to ensure the safest possible experience for themselves and their babies during labour and birth. Caregivers have a responsibility to provide the highest quality care and efforts should be made continuously towards improvement. One focus for improvement in perinatal care is the lack of attention given to maintaining fluid balance when intravenous therapy (IV) is administered during labour.

For the 377,000 women who give birth annually in Canada, intravenous therapy during labour is a widespread practice (Statistics Canada, 2009, http://www40.statcan.gc.ca/l01/cst01/demo04a-eng.htm?sdi=birth). Fluid administration is used as a preload for epidural analgesia, given as a bolus for abnormal fetal heart rate tracings (as defined by the Society of Obstetricians and Gynaecologists of Canada, (http://www.sogc.org/guidelines/public/112E-CPG1-March2002.) as a fetal heart rate < 110 or > 160 bpm, a changing fetal heart rate or decelerations, and for elevated maternal temperatures. Additional intravenous fluid is given during the course of labour as a vehicle for medication administration, as a background infusion while epidural analgesia is in-situ, and in the event of a caesarean section or intrapartum complications, such as hemorrhage.

Fluid overload is one of the risks related to IV fluid therapy in labour. The exact prevalence of intrapartum fluid overload is not known but the risks associated with this outcome have been described. Cotton, Gonik, Spillman & Dorman (1984) reported that following normal pregnancy, colloid osmotic pressure is decreased in the postpartum period to sometimes dangerous levels and this decrease has been linked to the administration of intravenous crystalloid solutions. In this study, 72 low risk women who had been ordered IV crystalloids to
run at 125 to 150 millilitres (mls) per hour received volumes infused at twice that rate, indicating the lack of attention paid to the volumes of fluid infused to low risk women in labour.

Physiologic changes accompany fluid overload. Coronary arterial oxygen capacity decreases in response to the hemodilution that occurs following large volumes of infused fluid (Carvalho & Mathias, 1994). Intravenous infusions can lead to elevated central venous pressure after the administration of only one to two litres of fluid (Carvalho & Mathias, 1994). Fluid overload has also been associated with increased cardiovascular work, myocardial ischemia and pulmonary edema (Carvalho & Mathias, 1994; Sciscione, Ivester, Largoza, Manley, Shlossman, & Colmorgen, 2003). Serum levels of neuropeptides such as Atrial Natriuretic Peptide and Brain Natriuretic Peptide rise to facilitate natriuresis (Friese, Dineen, Jennings, Pruitt, McBride, Shafi, Frankel & Gentilello, 2007).

The effects of intrapartum fluid overload may not be limited only to the mother. It has been reported that intrapartum fluid affects the newborn as well, and this is evidenced by exaggerated weight loss in the fluid overloaded newborn (Keppler, 1988; Livingstone, Willis, Abdel-Wareth, Thiessen & Lockitch, 2000). Other fluid volume related complications in the newborn may include edema, neonatal respiratory distress and acidosis (Behat, Lewis, David & Liza, 2006; Carvalho & Mathias, 1994; Elgart, 2004; Lind, 1983; Morton, 1993; Roth, 1969; Wasserstrum, 1992a; Wasserstrum, 1992b).

Breastfed newborn weight loss > 7% is a cause of clinical concern, based on the recommendations from the International Lactation Consultants’ Association (1999) and the Academy of Breastfeeding Medicine (2007) that identify weight loss > 7% as a marker for unsuccessful breastfeeding. This degree of weight loss has been associated with an increased risk of hypernatremia in the first few days of life (Uraas, Karadag, Dogan, Tonbul & Tatli,
The fluid overloaded newborn may lose additional fluid during this time and may be erroneously identified as an ‘at risk’ breastfed infant who has lost a clinically significant amount of weight. When weight loss reaches such levels, interventions are introduced to try to limit weight loss and to promote the initiation of breastfeeding. This unrecognized diuresis may lead to unnecessary interventions to limit weight loss that may include the introduction of artificial baby milks that could undermine the development of an adequate breastmilk supply. Other interventions may include breast pumping and additional health care visits that may lead to mothers’ discouragement and decreased confidence. Importantly, maternal confidence has been positively associated with breastfeeding duration and exclusivity (Dennis, 1999). Given the concerns about breast milk production and newborn weight gain, discharge may be delayed for these families placing additional burden on the health care system. Newborn weight loss is the driver for other interventions and puts at risk women’s decisions to continue breastfeeding. The initiation of breastfeeding could be protected by preventing iatrogenically imposed, exaggerated weight loss.

**Problem Statement**

Approximately 59% of labouring women in the province of Ontario receive epidural analgesia and therefore have intravenous therapy initiated during labour (Chapman, 2007), yet there are no published protocols or guidelines available to address fluid management in labour to optimize care for women and their infants. There is inadequate evidence on which to base clinical recommendations for intravenous fluid management during labour.

A Cochrane review, *Restricting Oral Fluid and Food Intake During Labour* aimed to determine the benefits and risks of food and fluid restriction during labour with or without
intravenous therapy (Singata & Tranmer, 2010). The authors concluded that IV therapy predisposed women to an increased risk of fluid overload and they called into question the value and safety of routine IV treatment.

The absence of an evidence-based approach to intrapartum fluid management can result in fluid overload, with consequent maternal and newborn complications. Potential maternal complications include altered fluid and electrolyte status and pulmonary edema. Potential neonatal complications include exaggerated newborn weight loss, supplementation with artificial baby milks, compromised breastfeeding, increased health surveillance and prolonged hospital stays (Behat, et al., 2006; Carvalho & Mathias, 1994; Keppler, 1988; Livingstone et al., 2000; Sciscione et al., 2003).

An intervention to guide fluid management in labour has the potential to improve fluid balance and health outcomes for women and their newborns. An evidence based intrapartum fluid management protocol may reduce the proportion of infants who lose > 7% of their birth weight and the associated consequences of exaggerated weight loss. A randomized controlled trial evaluating a protocol based approach to fluid management in labour could help close the gap regarding the value and safety of IV therapy.
Chapter Two

Review of the Literature

The literature review will focus on intrapartum fluid requirements, IV fluid administration in surgical and obstetrical populations, risks associated with fluid overload such as pulmonary edema and exaggerated newborn weight loss, as well as physiologic measures of fluid overload. The relationship between newborn weight loss and breastfeeding outcomes will also be reviewed.

Intravenous Fluid Requirements

Routine intravenous fluid management in the adult has been associated with morbidity and mortality related to its use, including pulmonary edema, altered electrolyte status (Cotton, Gonik, Spillman & Dorman, 1984; Elgart, 2004; Seiscone, Ivester, Largoza, Manley, Sholssman & Colmorgen, 2003; Singhi & Chookang, 1984; Spencer, Mann, Smith & Wolfson, 1981). Risks have been identified and recommendations have been made for careful, conservative approaches to fluid administration and the development of protocols to guide this practice (Brandstrup, 2006).

Intravenous fluid therapy in surgical populations.

Six randomized controlled trials were reviewed that evaluated routine versus conservative fluid protocols for surgical patients (Brandstrup, Tenneson, Beir-Holgersen, Ording, Larsen, Ramussen et al., 2003; Holte, Jensen & Kehlet, 2003; Holte, Klarskov, Christensen, Lund, Neilsen, Bie & Kehlet, 2004; Holte, Kristensen, Valentiner, Foss, Husted & Kehlet, 2007; Lobo,
Bostock, Neal, Perkins, Rolwand & Allison, 2002; Nisanevich, Felsenstun, Almogy, Weissman, Einau & Matot, 2005) (see Appendix A, Evidence Tables for Fluid Management in Surgical Populations). Pulmonary function, weight gain, wound healing; bowel function and length of stay were among the outcomes evaluated.

Brandstrup et al. (2003) examined the efficacy of a conservative fluid protocol on tissue healing and cardiopulmonary complications. Patients in their sixth decade, undergoing colorectal resection, were randomized to standard or conservative fluid regimens (n=172). Post operative complications were significantly reduced in the conservative fluid group. There was a dose response relationship between fluid volume and complications ($p<0.001$). Tissue healing complications were decreased ($p<0.04$) and cardiopulmonary complications were reduced ($p<0.007$). This work established the link between intraoperative fluid overload and morbidity.

Holte, Jensen and Kehlet (2003) found similar responses in a double blinded, randomized trial in a healthy elderly population undergoing elective bowel surgery. A significant improvement in pulmonary function, as measured by forced vital capacity and forced expiratory volume in one second, was noted for the group that received conservative infusions based on 5 ml/kg versus 40 ml/kg ($p<0.05$). Urine output was significantly less in the 5 ml/kg group at all time points between surgery and the first 24 hours in the post operative period ($p<0.05$). There was a significant weight gain at 24 hours post infusion in the 40 ml/kg group ($p<0.05$). Sample size was limited to twelve participants and there is no report of a power calculation to justify this sample size, so power may be lacking to draw any conclusions. However, the delay reported in excreting fluid 24 hours post infusion may be an indication of the time it takes to re-establish normohydration.
Lobo (2002) furthered our understanding of the morbidity associated with intravenous fluid overload through a randomized trial involving uncomplicated surgical patients, where one group received three litres of fluid per day and the other group received less than two litres of fluid (conservative fluid group). Solid and liquid gastric emptying times were significantly shorter in the conservative fluid group ($p<0.03$ and $p<0.02$ respectively). The conservative fluid group was discharged three days earlier than the three litre per day group ($p<0.001$).

More recently, Holte, Fosso, Andersen, Valentin, Lund, Bie and Kehlet (2007) compared the effect of liberal and restrictive fluid regimens on 32 fast-track colonic surgery patients and found that the median fluid volume of 640 ml in the restrictive group resulted in transient improvement in pulmonary function post operatively, compared to median volumes of 5050 ml in the liberal group ($p<0.05$).

In another trial of a conservative versus liberal fluid protocol, in adult surgical patients ($n=152$) undergoing elective intra-abdominal surgery, significantly fewer patients developed complications in the conservative fluid group ($p<0.04$) (Nisanevich, Felsenstun, Almogy, Weissman, Einau & Matot, 2005). Patients in the conservative fluid group had shorter lengths of stay and earlier return to bowel function.

Other studies highlight the need for an evaluation of fluid management in surgical populations. Lowell, Schifferdecker, Driscoll, Benotti, & Bistrian,‘s (1990) work identified the morbidity associated with intravenous fluid overload. In this prospective, descriptive study, 40% of patients had a 10% weight gain during the peri-operative period ($n=48$) related to excessive fluid administration. In another study, 60 patients were randomly allocated to receive or not receive IV fluids during surgery (Janvrin, Davies & Greenhalgh, 1980). The group that received fluids was significantly more hemodiluted and hypercoagulated than the group that received no
fluid ($p<0.001$), and the incidence of postoperative deep vein thrombosis occurred significantly more often in the fluid group ($p<0.05$). In a retrospective case cohort study of 100 consecutive patients undergoing elective colonic or rectal resection, volumes of intravenous and oral intake were recorded from the day of surgery until the fifth postoperative day (Tambyraja, Sengupta, MacGregor, Bartolo & Fearon; 2004). Patients who received a smaller volume of post operative intravenous fluid (1.8L vs 2.1L daily) had fewer complications ($p<0.05$).

Conservative IV fluid therapy has consistently been shown to improve outcomes in low risk, adult patients undergoing elective, major gastrointestinal surgical procedures. Outcomes associated with conservative fluid protocols included decreased length of stay, earlier return to bowel function (Brandstrup et al., 2003; Lobo et al., 2002; Nisanevich et al., 2005) and improved pulmonary function (Brandstrup et al., 2003; Holte et al., 2003; Holte et al., 2007; Lobo et al., 2002).

The 2007 Cochrane Review, *Perioperative Fluid Volume Optimization Following Proximal Femoral Fracture* (Price, Sear & Venn), highlighted the importance of developing approaches to optimize fluid volume. Four trials were included in this review, of which two studies involving a total of 130 patients, were of adequate quality. These trials evaluated invasive hemodynamic monitoring rather than protocol led approaches to fluid management. In both trials, invasive monitoring led to significant increases in fluid volumes infused and reductions in lengths of stay. However, the typical hip fracture patient is over 80 years old and often presents to hospital in a dehydrated state requiring correction of hypovolemia. Reviewers cautioned that while length of stay was reduced, effects on other important, longer-term outcomes are unknown. This review supported the need for the rigorous evaluation of methods to optimize intravascular fluid volume and the use of systematized, protocol guided
interventions. Conclusions were that invasive methods to optimize fluid during surgery may shorten hospital stay for this group of patients. However, since follow up was short term and fluid administered was not protocol guided, conclusions are cautionary. Price et al. (2007) recommended the development of protocols to guide fluid therapy.

In summary, the Cochrane review (Price et al., 2007) provided support for increased fluid administration. However, these surgeries were non-elective and involved the frail elderly, who were perhaps dehydrated prior to surgery. No trials were found evaluating the effects of conservative fluid therapy on populations undergoing other types of surgery. Conservative IV fluid therapy, defined as replacing only fluid losses, has been shown to improve outcomes in healthy adults undergoing elective, major surgical procedures (Brandstrup, et al., 2003; Holte, Jensen & Kehlet, 2003; Holte et al., 2004; Holte et al. 2007; Janvrin et al., 1980; Lobo et al., 2002; Nisanevich et al., 2005). It is yet to be determined if conservative approaches to intrapartum fluid management for low risk women improve outcomes as well.

**Intrapartum fluid management.**

While the routine approach to fluid management in labour is an unrestricted one, Carvalho and Mathias (1994) challenged conventional thinking by identifying the obstetrical patient as already over hydrated. The risks and benefits of administering a large amount of fluid to a woman with increased body water content, an expanded plasma volume and a potentially overstressed cardiovascular system are controversial (Carvalho & Mathias, 1994). Since fluids administered to labouring women are rapidly equilibrated with the fetus and given the labouring woman’s overhydrated state, it is surprising that clinical practice is focused on preventing problems related to dehydration of the labouring woman rather than fluid overload. The concept
of overloading on intravenous fluids in labour was described by Newton (1988) over twenty years ago, and has been minimally examined and not yet resolved. Development of a conservative, fluid balanced, approach to fluid administration is a physiologically sound approach to intrapartum care.

A systematic review was conducted by the author and an interprofessional committee that focused on fluid management in labour and included the review of abstracts of systematic reviews and randomized controlled trials. We searched the Cochrane Pregnancy and Childbirth Group Trials Register (August 2009), limiting the search to trials that were published between 1986 and 2009, and were written in the English language.

The primary search consisted of CINAHL, MEDLINE and EMBASE databases. All searches except the hydration search were identified from the Cochrane Database of Clinical Trials for Pregnancy and Birth, http://ehp.sagepub.com/cgi/content/abstract/18/4/428 (Appendix B). All elements of the primary search used the Cochrane terms for pregnancy and childbirth and fluid search terms developed by JW (Appendix B). Four sub-searches were focused on epidural analgesia, fever, fetal heart rate and hydration assessment. Titles and abstracts were reviewed for inclusion by two individuals (JW and AA) based on criteria specified prior to the search. Criteria included low risk women, in labour, receiving IV therapy with outcomes of interest including maternal, fetal or newborn well-being. Disagreements between the two reviewers were resolved by consensus. The same search strategy was also used to identify case control and cohort studies.

The studies included in the systematic review were also analyzed individually. Evidence tables were generated to summarize the systematic review and randomized trials (Appendix C).
A total of 2,274 randomized trials and systematic reviews were found after search terms for pregnancy and childbirth identified by the Cochrane Collaboration and the fluid search terms were applied.

**Figure 1: Systematic Review Search Strategy**

- Cochrane Pregnancy and Childbirth Search terms
- Fluid Hedge*
- Epidural
- Fetal heart rate
- Fever

- 312 Systematic Reviews 1191 RCTs
- 82 Systematic Reviews 468 RCTs
- 59 Systematic reviews 162 RCTs

Inclusion criteria applied: maternal, fetal or neonatal outcomes

- 1 Systematic Review 5 RCTs
- 1 Systematic Review 6 RCTs
- 0 Systematic Reviews 0 RCTs

*hedge refers to the filter focused on fluid terms that was created for this search

Individual searches followed for epidural analgesia, fetal heart rate and fever. After inclusion criteria were applied, one systematic review and eight randomized trials were identified.
in total with some duplicates in the epidural and fetal heart rate searches. Four randomized trials in the systematic review that met search criteria were also evaluated individually. Of the six trials contributing to the Cochrane Review (Hofmeyr, 2009), one was based on an abstract for which adequate detail was unavailable even after attempting to contact the primary author by email. The other trial not included in this review was published prior to 1986 and used high dose epidural analgesia which is no longer routine practice. A subsequent search conducted for case control and cohort studies, using the same search criteria, did not identify any articles meeting the inclusion criteria.

Two randomized controlled trials evaluated the effect of two fluid rate regimens on the length of low risk labour, use of oxytocin and caesarean section rates (Eslamian, Marsoosi & Pakneeyat, 2006; Garite, Weeks, Peters-Phair, Patillo & Brewster, 2000). In both studies, women were randomized to receive an IV infusion of either 125 mls per hour or 250 mls per hour during the course of labour. The analysis found that the incidence of “prolonged” labour, defined as labour length greater than 12 hours, was significantly higher in the 125 mls per hour groups ($p<0.0001$ and $p<0.04$ respectively). There was a trend towards the use of oxytocin in the 125 mls per hour group in Garite’s (2000) study and a significant difference in Eslamian’s (2006) study ($p<0.001$). There was a trend towards a decreased incidence of caesarean sections in both studies. In Garite’s (2000) study, the mean total of fluid infused in the 125 mls per hour group was 2008 mls and the mean total in the 250 mls per hour group was 2483 ml, resulting in a difference of mean total volumes infused of 475 mls. The resulting difference of mean total volumes infused in Eslamian’s (2006) study was 255 mls. It is difficult to make a physiologic argument for such small amounts of fluid impacting clinical outcomes.
Another randomized controlled trial compared intrapartum normal saline infusion with infusions of 5% and 10% dextrose to determine the effect on length of labour, oxytocin use and caesarean section rates (Shrivastava, Garite, Jenkins, Saul, Rumney, Prslicka & Chan; 2009). Nulliparous women in spontaneous labour at term were randomized to one of three fluid solutions. Authors report a significantly shorter length of labour in women receiving dextrose solutions \((p < 0.02)\). However, it was the length of the second stage of labour rather than the time to full dilatation that was shorter. Of concern is the censure of any women randomized who delivered by caesarean section. Excluding these women raises concern about reporting bias. As well, the authors note a trend towards an increased rate of caesarean section in the dextrose infusion groups. Since it cannot be determined which woman will require an intrapartum caesarean section, it is questionable whether shortening the length of labour with dextrose infusions while increasing the risk of caesarean delivery is advantageous. Reports of concerns related to inducing hyperglycemia in the mother and the newborn with intrapartum infusions of dextrose are not fully addressed in this trial.

The prevention of hypotension and fetal heart rate deterioration by administering an intravenous fluid preload prior to an epidural analgesia was evaluated in five randomized trials and in a Cochrane Systematic Review (Hofmeyr, 2009). Four of the five trials evaluated were also included in Hofmeyr’s (2009) review as well as an additional trial that was not included in the Cochrane review because there was no control group in the design. There were no studies found evaluating the effect of fluid bolus for treating hypotension, fever or the deterioration of fetal heart rate patterns.

Review of the five randomized trials revealed that samples were similar, and all women experienced uncomplicated pregnancies and labour. All trials evaluated the effect of
administration of intravenous fluid as a preload prior to epidural analgesia on the prevention of hypotension and fetal heart rate changes (Cheek, Samuels, Miller, Tobin & Gutsche, 1996; Kinsella, Pirlet, Mills, Tuckey & Thomas, 2000; Kubli, Shennan, Seed & O’Sullivan, 2003; Shannon & Ramanathan, 1998; Zamora, Rosaeg, Lindsay & Crossan, 1993). All trials reported similar findings of no difference in the incidence of hypotension or fetal heart rate changes regardless of the volume of preload, the rate of infusion or the epidural analgesia dosage. No trials addressed the outcome of fluid overload or determined whether women and babies receiving routine IV therapy do better than women and babies receiving conservative fluid administration.

Only Zamora’s (1993) trial was adequately powered to detect differences in hypotension or fetal heart rate changes. However, there was no usual care group in Zamora’s design comparing preload volumes of 500 mls and 1000 mls. In this trial of 92 women, the only significant difference between groups was a decrease in the frequency of contractions in the group receiving the one litre preload \((p<0.05)\). It is questionable whether there is a clinically significant difference between volumes of 500 mls and 1000 mls to have been able to show a difference in outcomes between these groups.

**Cochrane Review Preloading for Epidural Analgesia**

Hofmeyr revised the Cochrane Systematic Review “Prophylactic Preloading for Regional Analgesia in Labour” in 2009 and included six trials. This systematic review contained relevant randomized trials following the standardized, rigorous Cochrane protocol. Two of the trials in the review used high dose epidural analgesia regimens, two used low dose and two evaluated combined spinal epidural analgesia techniques. Low dose and high dose trials were considered
separately since high dose epidural analgesia is no longer common practice. Hofmeyr reported that issues of heterogeneity prevented a meta-analysis from being conducted as part of this review. He concluded that the sample sizes in the low dose studies were too small to show whether preloading was beneficial. Hofmeyr’s conclusion highlights the lack of evidence available to guide practice on the issue of preload prior to epidural analgesia.

One study that was not identified in Hofmeyr’s (2009) review was aimed at evaluating IV fluid resuscitation during labour. The design used two volumes of fluid bolus and found an intravenous fluid bolus of 1000 mls was more effective than a 500 mls bolus in increasing fetal oxygenation (n=42, p< 0.03) (Simpson & James, 2005). Unfortunately, there was no rationale given for what a clinically significant difference in oxygen saturation would be and there was no usual care group in the design. Although the study was meant to evaluate the efficacy of interventions for fetal heart tracing decelerations, the results are speculative since no decelerations were present when the interventions were evaluated. Adverse effects related to total fluid volume infused were not reported in these studies. No studies addressed the outcome of fluid overload for low risk labouring women, the fetus or the newborn.

**Other Cochrane Reviews**

Hydration therapy has been used as a treatment for preterm labour based on the belief that dehydration is an underlying cause of premature labour contractions. Rehydration is thought to increase maternal blood flow and uterine blood flow thereby decreasing uterine contractility and the secretion of oxytocin. A Cochrane Review was conducted including randomized trials of women less than 37 weeks pregnant treated with intravenous solution versus oral hydration or no treatment (Stan, Boulvain, Hirsbrunner-Amagbaly & Pfister, 2002). The authors concluded that
there were insufficient data to support the use of hydration as a treatment for preterm labour. Treatment with intravenous therapy was not deemed beneficial for preterm labour in adequately hydrated women.

A Cochrane Review (Toohill, Soong and Flenady, 2008), *Interventions for Ketosis During Labour*, attempted to assess the effects of intravenous fluid or increased oral intake intrapartum on maternal fetal and neonatal outcomes. The authors found no trials suitable for inclusion in the review. These Cochrane Reviews, focused on pregnancy care, did not provide direction about the most effective approaches to managing intravenous therapy in low risk and high risk populations. This lack of evidence reinforces the need to develop guidelines for fluid management in labour.

No guidelines or evidence based practices were found regarding the assessment of fluid status of pregnant or labouring women. Currently, there is insufficient evidence to identify the most effective strategy for intravenous fluid management during low risk or high risk labour. Efforts to identify an optimal IV infusion rate have been hampered by methodological limitations. A systematic review addressing one reason for fluid administration, preload for epidural analgesia was not able to conclude that preloading was beneficial. There are only case reports and anecdotal evidence of adverse events related to fluid administration (Cotton, Gonik, Spillman & Dorman, 1984; Elgart, 2004; Sciscone, Ivester, Largoza, Manley, Sholssman & Colmorgen, 2003; Singhi & Chookang, 1984; Spencer, Mann, Smith & Wolfson, 1981).

The evidence is not adequate to determine the existence and magnitude of a causal connection between a fluid management strategy and outcomes of fluid overload on maternal and fetal well being. There is inadequate evidence to connect the strategy of fluid management of preload for epidural analgesia with prevention of hypotension and fetal heart rate changes.
There is only indirect and anecdotal evidence connecting fluid management in labour with adverse outcomes for women and newborns.

In light of the lack of evidence supporting routine fluid administration, the risk of limiting fluid in healthy, adequately hydrated women needs to be evaluated along with the risk of iatrogenic fluid overload, but the extent of this risk has never been evaluated or quantified.

**Hormonal Markers of Fluid Overload in the Fetus: Brain Natriuretic Peptide**

One approach to quantifying the extent of fluid overload is through the use of serum measures. Serum Brain Natriuretic Peptide (BNP) and Atrial Natriuretic Peptide (ANP) are two such serum markers that can be measured in cord blood. ANP and BNP are hormones released from the cardiac myocytes that counteract the effects of fluid overload through their action on the adrenals, kidneys and blood vessels (Friese, Dineen, Jennings, Pruitt, McBride & Shafi, 2007). Glomerular filtration rate is increased by afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction. Peptide receptor binding results in natriuresis, the excretion of sodium and water through the inhibition of aldosterone secretion and a decrease in blood pressure through vasodilation and suppression of sympathetic responses (Friese et al., 2007).

Due to its stability, NT-proBNP, BNP’s inactive form is commonly used for laboratory analysis. NT-proBNP has been used in adult populations to diagnose heart failure (Clerico, Fontana, Zyw, Passino & Edmin, 2007; Collins, Riaba-Bentle & Storrow; 2003; Shah, Nolan, Rao, Wang, Christenson & Shanholtz, 2007) and levels have been found to be elevated in pregnancy induced hypertension (Tihtonen, 2007).

Levels of ANP and NT-proANP in maternal and cord plasma were measured to identify the impact of spontaneous labour without IV fluids, and caesarean section with IV fluid load
Maternal and cord blood concentrations of NT-proANP were higher after elective caesarean section than after spontaneous vaginal birth ($p < 0.04$ and $p < 0.02$ respectively). The authors concluded that IV volume load and labour stress stimulate the release of natriuretic peptides. However, the sample sizes were small for both caesarean section ($n=15$) and spontaneous delivery ($n=20$). It is not reported how labour stress was identified as a factor affecting NT-proANP levels. It would seem that this conclusion is tentative, at best. The authors recommended the use of NT-pro-ANP as a marker of changes in intravascular volumes, and yet it has been established that BNP levels are more sensitive to acute volume changes whereas ANP is a more useful measure for states of chronic volume stress (Walther, Stepan & Faber, 2001).

Folk, Lipari, Nosocitch, Silverman, Carlson & Navone (2005) conducted a review of 17 charts to determine if BNP levels provide information regarding ventricular function in obstetrical patients with acute dyspnea. BNP levels were elevated ($>100$ pg/ml) in five of six patients identified with fluid overload. It was found that BNP levels responded rapidly to fluid overload, within minutes to hours after infusion. This makes the timing of sampling appropriate since a NT-proBNP response in this trial could be expected to be seen in cord blood at delivery.

Walther et al. (2001) collected fetal blood samples during cordocentesis from 18 fetuses, nine controls and nine isoimmunized fetuses, receiving intravascular transfusion. ANP and BNP levels were significantly higher in control and isoimmunized fetal samples than maternal samples ($p < 0.05$). While isoimmunized fetuses demonstrated chronic fluid overload with elevated levels of ANP, the short term response to the volume load of the transfusion resulted in a significant rise of only BNP ($p < 0.05$). If BNP captures acute changes in fluid loading and ANP captures
chronic changes, BNP would be the more appropriate measure for determining changes in
venous cord blood related to intrapartum fluid infusion.

Reference values for NT-proBNP, a more stable marker of BNP, were established in cord
blood by Schwachtgen et al. (2005) based on 62 serum samples obtained at delivery. There was
no statistical difference between arterial and venous umbilical cord blood values. The mean NT-
proBNP cord blood level was 818 pg/ml, (± 546). Cord blood levels and newborn levels were
high compared to older children and healthy adults, reflecting the circulatory changes in the
perinatal period, including the exposure of the left ventricle to elevated volume and pressure load
at birth (Schwachtgen et al.). While several studies have established the sensitivity and
specificity of NT-proBNP to detect heart failure, there are no such measures for fluid overload in
cord blood samples (Worster, Balion, Hill, Santaguida et al., 2008).

Characteristics that make NT-proBNP the preferred marker of fluid overload in the
intrapartum period are its longer half life and its strong correlation with acute versus chronic
fluid overload. NT-proBNP’s half life is much longer than the half life of BNP (<30 minutes
versus > 90 minutes) and so more practical for measurement (Clerico, Fontana, Zyw, Passino &
Emdin, 2007; Colucci & Chen, 2007; Daniels & Maisel, 2007). Datta et al. (1991) suggested
that fetal neuropeptide levels may be able to provide important information about fetal well-
being. It is not known if NT-proBNP levels are elevated in cord blood samples of newborns
whose mothers receive usual fluid management intrapartum. Cord serum levels could be useful
in determining whether a conservative fluid protocol maintains normal fetal NT-proBNP levels,
avoiding a fluid overload response.
**Risks Associated with IV Fluid Overload**

Adverse events following fluid overload such as edema, shortness of breath and weight gain are not reported in obstetrical cases but are reported in surgical populations. Serious complications such as pulmonary edema are reported but are rare occurrences in this population.

**Pulmonary edema.**

The increased risk of pulmonary edema related to childbirth is due to several factors including the autotransfusion that increases cardiac output by 10-20% immediately postpartum as blood is shunted from the uterus into systemic circulation, the mobilization of interstitial fluid into the bloodstream and the postpartum fall in colloid osmotic pressure (Wasserstrum 1992a). When fluid overload does occur during the intrapartum period, the effects may continue for several days postpartum (Lind, 1983).

Pulmonary edema can be a life threatening obstetrical complication occurring in approximately 1 in 1000 births (Sciscione et al., 2003). This complication occurs when an excess accumulation of fluid in the pulmonary interstitial and alveolar spaces prevents proper diffusion of oxygen and carbon dioxide. The excess fluid interferes with oxygenation and can lead to hypoxemia (Poole, 2003). During pregnancy, pulmonary edema is commonly associated with fluid and blood replacement therapy and 11% of maternal deaths were related to pulmonary complications in one report (Poole, 2003). Three published reports of pregnancy related pulmonary edema summarized 122 cases, including five maternal deaths (Huang & Williams, 2002, Sciscione et al., 2003, Zhang et al., 2001). In Zhang et al.’s (2001) review, five of 29 cases of pulmonary edema were related to intrapartum intravenous infusion management, two cases to rapid infusion postpartum and six to aggressive infusion to treat hypovolemia. Sciscione
et al. reported that 22% of the cases of pulmonary edema in their review were caused by fluid overload. Women with pulmonary edema had a mean positive fluid balance of 6022 mls compared to 1017 mls given to women who did not develop pulmonary edema ($p<0.003$).

Arieff (2007) reviewed 13 cases of fatal post operative pulmonary edema in surgical patients. These patients had received an average of 171 ml/kg/day of intravenous fluid or 4.5 litres per day. Arieff (2007) recommended that fluid volumes not exceed 67 ml/kg/day and highlighted that there is no established “panic value,” i.e. a volume of fluid that, having been infused, is considered excessive and should attract caregiver attention. He recommended that panic values be established.

Samol & Lambers (2005) conducted a retrospective case control study of 150 antenatal patients receiving treatment for preterm labour with magnesium sulfate. Women who developed pulmonary edema had greater IV infusion rates than the women who did not experience pulmonary edema. Samol & Lambers (2005) recommended limiting total daily intake to 2500-3000 mls. The study’s conclusion was that both magnesium sulfate and IV fluid are risk factors for pulmonary edema in pregnancy.

**Oxytocin’s role in fluid overload.**

Induction with IV oxytocin is another potential contributor to fluid overload. Oxytocin’s action resembles that of antidiuretic hormone and through this action may contribute to fluid retention. Oxytocin’s antidiuretic effect is considered to be mild, but dose related and high doses of oxytocin (> 20 mU/min) have been associated with fluid overload (Joo, Kim, Park, Oh, Kim, Ahn, Kin, Lee, Han, 2007; Shyken & Petrie, 1995). Reports of fluid overload, however, have occurred in cases where oxytocin was administered in a now obsolete practice of using
electrolyte free intravenous solutions. It is not clear whether the absence of sodium, the antidiuretic action of oxytocin, or the combination of the two, resulted in the hyponatremia reported (Joo et al., 2004; Ophir, Solt, Odeh & Bornstein, 2007). Oxytocin is thought to contribute to fluid overload, yet its effect may only be felt at high dosages.

**Summary of the Literature Related to Intravenous Administration**

The tendency towards fluid overload during intrapartum care follows concerns that labouring women are at risk for dehydration and ketosis. It is not clear that these concerns are well founded and there are no well established practices for measuring fluid status. Women usually begin labour in a positive fluid state and there is no evidence to support liberal intrapartum fluid administration practices.

**Intrapartum Fluid Administration and the Newborn**

Concern for the risks of fluid overload should not be limited to the labouring woman. The fetus is also a recipient of the fluid volume given intrapartum. When fluid volume exceeds physiologic need, the newborn may be affected as evidenced by altered biomarkers and increased weight loss in the early postpartum period. This may be particularly noticeable in the breastfed newborn and may impact the initiation of breastfeeding.

**Breastfeeding**

Breastmilk is considered the ideal food for infants, providing perfect nutrition and protection against illness, as well as health benefits for mothers. The long term and short term benefits are well supported in the literature. Benefits include reduced infant morbidity from
respiratory, urinary tract, and ear infections, as well as gastrointestinal disease (Aniansson, Alm, Anderson, Hakansson, Larsson, Nylen, 1994; Cesar Victora, Barros, Santos & Flores, 1999; Howie, 1990; Marild, Hansson, Jodal, Oden & Svedbery, 2004;). Protection against juvenile diabetes, elevated blood pressure and obesity are also associated with breastfeeding (Fewtrell, 2004; Sadauskaite, 2004; Singhal, Cole & Lucas, 2001; Taittonen, 1996; Virtatnen, Rasanen, Aro, Lindstron, Sippola & Lounamaa, 1991; Wilson, Forsyth, Grenne, Irvine, Hau, Howie, 1998). The World Health Organization (2001) recommends the promotion and protection of breastfeeding, advocating exclusive breastfeeding as the optimal practice for the first six months of life. Health promotion initiatives include targets for increasing breastfeeding exclusivity, yet, in a 2009 United States survey, 26% of babies received formula before they were two days old (http://www.cdc.gov/breastfeeding/data/report_card.htm).

A 2009 national survey of Canadian women’s breastfeeding practices reported that while 90% of women initiate breastfeeding, at six months only 14.4% are exclusively breastfeeding and 54% are partially breastfeeding. These rates fall short of the goal of six months of exclusive breastmilk recommended for all infants (http://www.phac-aspc.gc.ca/rhs-ssg/survey-eng.php).

Given this significant decrease in exclusive breastfeeding in the first week of life, it is important to identify ways to promote breastfeeding in the early days and to understand reasons why women quit. Premature discontinuation of breastfeeding is often more the result of breastfeeding problems than the result of women choosing to quit and women who quit are disappointed that they have not breastfed longer (Barber, Abernathy, Steinmetz & Charlebois, 1997). Concern about early infant weight loss could lead to maternal concerns about insufficient milk supply, decreased breastfeeding self-efficacy and the decision to discontinue breastfeeding.
**Breastfeeding self-efficacy.**

Decreased confidence in one’s ability to breastfeed is associated with decreased self-efficacy and an increased likelihood of quitting (Dennis, 2003). Self-efficacy is the confidence an individual has in his or her perceived ability to perform a specific task or behaviour (Bandura, 1977). Self-efficacy includes outcome expectancy, the belief that a given behaviour will result in a particular outcome, and self-efficacy expectancy, the conviction that one can perform certain task or behaviours successfully to produce desired outcomes (Bandura, 1977). It follows, then, that if a woman believes she can breastfeed and is determined to do so, she is likely to succeed. In contrast, if a newborn is identified as losing a clinically significant amount of weight and this lessens a mother’s conviction that she can breastfeed, she is more likely to quit breastfeeding.

Breastfeeding self-efficacy has been studied by Dennis and is considered to be an important variable affecting breastfeeding duration (2007). Factors that showed the strongest correlation with breastfeeding self-efficacy scores were women’s perceptions of breastfeeding progress, whether the infant feeding method was the one that the woman had planned on, and the mother’s satisfaction with the method of feeding (Dennis, 2006). It is questioned whether these factors could be positively affected by conservative fluid management in labour.

**Early Newborn Weight Loss**

A certain amount of weight loss is expected for all newborns in the early postpartum period (Dewey, Nommsen, Henig & Cohen, 2003; Keppler, 1988; MacDonald, Ross, Grant & Young, 2003; Tarnow-Mordi, Shaw, Liu, Gardner & Flynn, 1981). The Academy of Breastfeeding Medicine (2007) and the International Lactation Consultants’ Association (1999) caution that weight loss > 7 percent is a sign of ineffective breastfeeding indicative of inadequate
milk production. Further support for the marker of 7% weight loss being clinically significant is the average weight loss reported in three descriptive studies was < 7% (Dewey et al., 2003; Macdonald et al., 2003; Marchini; 1997; Martens & Rompfh, 2007).

Efforts to support breastfeeding by minimizing weight loss would be a positive component of quality perinatal care. Women worry about their babies’ weight loss, their milk supply and wonder if they should continue breastfeeding (Dewey et al., 2003; Kearney, Cronenwett & Barrett, 1990). These concerns are well founded since many factors affect breastfeeding duration. Nulliparous women who receive epidural analgesia and IV therapy have been shown to have shorter breastfeeding duration than other women, indicating some possible relationship between the fluid administered, epidural analgesia and breastfeeding outcomes (Henderson, Dickinson, Evans, MacDonald & Peach, 2003). Women whose infants lose a clinically significant amount of weight in the first few days of life may be so concerned about their milk supply that they may decide to quit breastfeeding.

Dahlenburg, Burnell & Braybrook (1980) studied weight loss in 309 infants born to women with and without intravenous therapy during labour, 106 in the intravenous therapy group. Weight loss was greater in babies born to women receiving IV fluid during labour (p<0.01). Mean weight loss for babies whose mothers received IV fluids was 6.17 % (± 3.36) compared to the mean weight loss in the oral fluid only group of 4.07% (± 2.2). Since weight loss > 7 percent is associated with negative breastfeeding outcomes, this difference could be clinically significant for some infants.

Tarnow-Mordi, et al. (1981) initially described the theory that fluids given to the mother affect the newborn. In this descriptive study, designed to identify determinants of infant hyponatremia when labouring women received intravenous therapy, 95 mother infant pairs
participated. Women who received oxytocin and epidural analgesia received an average infusion of four to seven litres per day. Maximum postpartum weight loss for infants of mothers who received only oral fluids in labour was 3.6% (±0.2), for mothers receiving intravenous and oxytocin, 5.4% (±0.6), receiving intravenous and epidural analgesia 5.1% (±0.6), for mothers receiving intravenous fluids, and oxytocin and epidural analgesia, 6.4% (±0.5). It is not known whether these infants were breastfed or received artificial baby milk. Regardless of how the babies were fed, Tarnow-Mordi et al. (1981) concluded that excess weight loss was a possible consequence of fluid administration.

In a prospective, observational cohort study of 971 consecutive term newborns (Macdonald, Ross, Grant & Young, 2003), the median weight loss for breastfed infants was 6.6% (range 6.3-6.9), and the median time for maximum weight loss was 2.7 days. Another prospective cohort study of 961 term infants found that 3% of newborn infants experienced weight loss >10% and maximum weight loss occurred between day two and three (Wright & Parkinson, 2003). This supports the timing of identifying the point of maximum weight loss within the first 48 hours of newborn life, prior to hospital discharge.

A study was conducted involving 328 new mothers whose breastfeeding behaviours were evaluated by lactation consultants during the first two weeks postpartum (Dewey et al., 2003). The authors described excessive newborn weight loss of >10% associated with primiparity, caesarean section, flat, inverted nipples, use of non-breastmilk fluids in the first 48 hours, a second stage greater than two hours, and the use of labour medication (with and without epidural administration). Lactation difficulties during the early postpartum period were associated with an increased risk of early termination of breastfeeding and lower success with subsequent children. Dewey et al. (2003) concluded that the administration of intravenous fluids increased
the hydration status of the newborn and led to greater weight loss in the early postpartum. Infants lost, on average, 5.5% (±3.8) of their birth weight; 12% of infants lost more than 10%.

A retrospective chart audit of 813 healthy term newborns determined factors related to newborn weight loss (Martens & Romphf, 2007). The chart audit included infants exclusively breastfed, partially breastfed, and those exclusively given artificial baby milk. Weight loss prior to discharge was highest in the exclusively breastfed group, 5.49% (± 2.60). Factors that were associated with significantly higher weight loss included higher birth weight, female sex, epidural analgesia use and longer hospital stay. In contrast to Dewey et al.’s (2003) findings, parity and type of delivery were not significantly associated with increased weight loss. Martens and Romphf (2007) suggested that the relationship between epidural analgesia use and weight loss may be attributable to intravenous fluid administered to the mother with resulting overhydration of the newborn, contributing to increased weight loss as the newborn diureses.

Karinen, Rasanen, Paavilainen, Alahuhta, Jouppila & Jouppila (1994) described the effects of preloading with crystalloid versus colloid intravenous solutions for caesarean section on maternal and fetal blood flow (15 ml/kg of crystalloid, then 1000 mls every 30 minutes until delivery) and concluded that excessive preloading may have deleterious effects such as respiratory disturbances in the mother and the fetus. Singhi, Chookang & Hall (1985) suggested that fluid loading could be related to transient tachypnea of the newborn. While concerns are expressed regarding possible morbidity associated with administering more fluid than is physiologically necessary, there is no clear evidence available on newborn outcomes.

While there is verification in surgical populations that conservative approaches to intraoperative fluid management improve outcomes for some elective procedures, conservative approaches to fluid management for intrapartum care have never been evaluated. The effects of
conservative fluid management on the mother would be difficult to measure given the use of outcome measures of weight gain and pulmonary function in surgical populations. These approaches do not lend themselves well to postpartum evaluation. Weight loss measurement would be confounded by the weight typically lost at delivery and pulmonary function is affected by pregnancy and perhaps by epidural analgesia. Therefore, it was appropriate to consider newborn outcomes to evaluate fluid overload and a randomized trial evaluating a conservative approach to intrapartum fluid management on newborn weight loss was needed.

**Conceptual Framework**

The conceptual framework for this study was based on the physiology of fluid management and highlighted the relationships between fluid overload, maternal fetal circulation and early newborn weight loss in breastfed infants.

Excess fluid is characterized by fluid shift into the extracellular space that results in edema and elevated levels of brain natriuretic peptide (Friese et al., 2007; Heuther & McCance, 2000). The fluid administered to the labouring woman is also administered to the fetus and too much fluid is believed to result in weight loss in the newborn (Carvalho & Mathias, 2004; Dahlenberg, Burnell, & Braybrook 1980; Dewey et al, 2003; Lind, 1983 Martens & Romphf, 2007; Tandrow-Mordi et al., 1983).

Clinically significant weight loss results in increased attention being paid to the newborn’s health status and feeding behaviours. Breastfeeding episodes for these infants are monitored with greater care. Weight loss > 7% is associated with poor breastfeeding outcomes, and therefore, with interventions to address weight loss such as supplementation with artificial baby milk, delayed discharge and referral to a breastfeeding clinic for ongoing follow-up
(International Lactation Consultants’ Association, 1999; Academy of Breastfeeding Medicine, 2005). These interventions become more concerning when the weight loss for fluid overloaded babies is not related to feeding problems, but rather to the normal process of diuresis that follows fluid volumes given intrapartum. The schematic summary of the conceptual framework, in Figure 2 depicts how a conservative fluid management protocol could impact newborn weight loss.

**Figure 2: Conceptual Model for the FILL Trial**

- IV fluid given during labour aimed at preventing excess fluid administration
- Maternal intravascular compartment not expanded
- Fetal intravascular compartment does not expand
- No fetal fluid overload
- BNP levels normal
- No natriuresis
- Normal newborn weight loss
Body water distribution impacts homeostasis. Water is distributed between intracellular and extracellular compartments. The extracellular compartment includes intravascular space and interstitial space. Water and electrolytes move between the intravascular and interstitial spaces based on Starling’s Law (Huether & McCance, 2000). Colloid osmotic pressure, generated by plasma proteins, keeps water in the intravascular space and counteracts the movement of water into the extravascular space. Fluid overload decreases colloid osmotic pressure and facilitates movement into the extravascular space resulting in weight gain and edema formation (Cooper & Moore, 1999).

The kidneys are the main controllers of fluid and electrolyte balance through the renin-angiotensin-aldosterone system (Heuther & McCance, 2000). The kidney secretes renin in response to decreased perfusion and decreased sodium. Renin binds to angiotension I which converts to angiotension II, producing vasoconstriction and aldosterone release which increases resorption of sodium and water (Huether & McCance, 2000). Fluid overload causes the release of Brain Natriuretic Peptide (BNP). This release interferes with the renin-angiotensin-aldosterone response resulting in the excretion of sodium and water from the kidneys in an effort to decrease fluid overload (Friese et al., 2007).

The pathway to maintain euvolemia is achieved through administering fluids based on physiologic need. Rose & Post, (2001) recommended a daily fluid intake for normal adults of 1600 mls per day, or 66 mls per hour. Cunningham (2005) recommended that a woman labouring with a normal term fetus in an uncomplicated pregnancy requires 60-120 ml per hour of fluid to combat dehydration and acidosis. Sullivan (1990) reported that an average adult requires 1500-2000 ml of water daily and recommended that fluid intake should match fluid losses.
A healthy, term pregnant woman has approximately two additional litres of fluid stored in her extravascular space (Lind, 1983; Carvalho & Mathias, 1994). Fluids given in labour add excess fluid volume to the woman and her fetus, contributing to edema and potentially affecting the newborn’s weight through weight loss. Lind (1983), Dewey et al. (2003), Keppler (1988), Martens & Romphf (2007), Tarnow-Mordi et al. (1981) and Dahlenburg et al. (1980) identified a greater percentage weight loss in newborns whose mothers had IV fluid, particularly infants born to women receiving epidural analgesia.

This framework is proposed for the evaluation of a conservative approach to fluid management in labour and the impact on newborn weight loss because the physiologic principles of fluid balance support the linkages between maternal intrapartum fluid overload and newborn weight loss.

Research Questions

**Primary research question:**

For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for intravenous fluid management versus usual care on breastfed newborns’ weight loss prior to hospital discharge?

**Secondary research question:**

For low risk women receiving epidural analgesia in labour, what is the effect of conservative fluid management versus usual care on: breastfeeding self-efficacy, breastfeeding clinic visits and the incidence of exclusive breastfeeding?
Other research questions:

For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for fluid management versus usual care on: venous cord blood NT-proBNP levels, venous cord blood pH values < 7.25, Apgar scores < 7 at 5 minutes, delayed discharge and admission to the Neonatal Intensive Care Unit (NICU)?
Chapter Three
Research Design and Methods

The Fluid in Low Risk Labour (the FILL Trial) was a single site randomized controlled trial comparing a conservative protocol of fluid management with usual care for low risk women receiving epidural analgesia in labour.

Development of the Intervention

Following completion of the systematic review, a transdisciplinary committee, consisting of the principal investigator, a staff nurse, an anaesthetist, a nephrologist, a generalist obstetrician and a maternal fetal medicine specialist was convened to develop the protocol that would serve as the intervention for this trial. Meetings of this guideline committee took place over the summer months of 2007. Consensus was reached regarding the quality ratings for the trials reviewed. The following guideline was created and informed the development of the intervention.

Recommendations for fluid management in uncomplicated labours.

We recommend that caregivers routinely include hydration status as part of their admission history and physical for labouring women. Ongoing assessment of hydration status following admission for low risk women in labour should guide decision making regarding the appropriate volume of fluid to be given for management of a particular problem (B-III).

Caregivers should keep meticulous intrapartum fluid balance documentation for all women in labour receiving intravenous fluids. Volumes infused
should be reconciled against the physiologic need for fluid and necessary adjustments made to ensure euvoemia (I-III).

We recommend that whenever the care of the labouring woman is being handed over to another caregiver, that the fluid volume already infused and the written fluid balance sheet be an explicit part of the handover report (A-III).

We make no recommendation for or against routinely administering fluid volumes in excess of 125 ml per hour to women experiencing uncomplicated labours. Evidence of the value of larger volumes being routinely administered is of fair quality but the balance of benefits and harms cannot be determined (A-I).

We make no recommendation for or against routine provision of intravenous preload prior to epidural analgesia administration. We found insufficient evidence of the role of intravenous preload in preventing hypotension or fetal heart rate deterioration and conclude that the balance of benefits and harms is not well enough established to justify a general recommendation, other factors may influence decision making (I-I).

We conclude there is no evidence to recommend for or against routinely providing intravenous fluid bolus to treat epidural analgesia related intrapartum fever or non-reassuring fetal heart rate patterns (fetal heart rate < 110 bpm or > 160 bpm or with variable or late decelerations, SOGC, 2007) in euvoemic, low risk women in labour. Evidence regarding fluid bolus for these reasons is lacking and the balance of benefits and harms cannot be determined, other factors may influence decision making (I-III). (Watson, Armson, Angle, Kung,
Usual Intrapartum Fluid Management

Usual intrapartum fluid management included the initiation of intravenous therapy prior to epidural analgesia administration or when intravenous drugs needed to be administered. Usual care involved infusing between 500 mls and 1000 mls of Ringers Lactate solution at the time of epidural analgesia initiation and from three to five liters of IV fluid administered throughout labour. Boluses of fluid, of 200 or more millilitres, were given for abnormal fetal heart rate tracings and maternal fever. Hourly infusion volumes were 125 mls per hour or greater.

Conservative Intrapartum Fluid Management

A conservative intrapartum fluid management protocol was administered to the conservative care group. This protocol assumed that care would be individualized to the labouring woman and would be reflective of the events of her labour. Based on the recommendations of Rose & Post (2001), Cunningham (2005) and Sullivan (1990), as well as the systematic review (Hofmeyr, 2009) women received between 250 to 500 mls of Ringers Lactate solution at the time of epidural analgesia initiation and the intravenous infusion continued at the hourly rate of 75 to 100 mls per hour. Fluid balance calculations were conducted and recorded every four hours. Reaching values for fluid infused > 2500 mls required the nurse to review the fluid management plan with the physician responsible for the woman’s care. Maternal fever was initially treated with acetaminophen rather than fluid bolus. Decisions regarding bolus for abnormal fetal heart rate patterns were at the discretion of the caregivers.
Setting

The setting for the FILL Trial was a tertiary perinatal centre in a large urban centre, Toronto, Ontario, where 3800 births take place annually. Approximately 75 nurses worked in the labour and delivery unit, which included an early labour assessment area.

Recruitment and Randomization

Women were recruited in the early labour assessment area and randomized when they decided to have epidural analgesia (Appendix E: The FILL Trial Maneuver). Following confirmation of eligibility and consent to participate, women were randomized into conservative or usual care arms. Randomization was achieved electronically through the use of www.randomize.net.

Inclusion Criteria

Women were eligible for inclusion when they presented in the early labour assessment area if they were sufficiently well hydrated (based on a history of no vomiting or diarrhea in the last 24 hours), and were considered to have a healthy pregnancy at “no predictable risk”, according to the Ontario Medical Association Risk Scoring Tool (Ontario Medical Association, https://www.oma.org/Forms/OntarioAntenatalRecord2005. Eligible women had completed 36 weeks and 7 days of their pregnancy and had no significant maternal medical disease, no prior perinatal morbidity or mortality and adequate fetal growth. Eligible women were anticipating a vaginal birth, planning on having epidural analgesia and intending to breastfeeding. Women were assessed to be in early or active labour.
**Exclusion Criteria**

Women were considered ineligible if they reported a history of vomiting or diarrhea in the last 24 hours, were multiparous and > 4 cm dilated, or primiparous and > 5 cm dilated or were expected to deliver within the next 4 hours. Women were also ineligible if they were not fluent in written and spoken English, had a history of breast surgery or if they were planning discharge before 48 hours.

**Outcome Measures**

The primary outcome for The FILL Trial was breastfed newborn weight loss based on the recommendations from the International Lactation Consultants’ Association (1999) and the Academy of Breastfeeding Medicine (2007) that identified weight loss > 7% as a marker for unsuccessful breastfeeding. The fluid overloaded newborn may lose additional fluid in the first few days after birth and may be erroneously identified as an ‘at risk’ breastfed infant who has lost a clinically significant amount of weight. When weight loss reaches such levels, interventions are introduced to try to limit weight loss and to promote the initiation of breastfeeding. This unrecognized diuresis may lead to unnecessary interventions to limit weight loss that may include the introduction of artificial baby milks which could undermine the development of an adequate breastmilk supply.

Other interventions may include breast pumping and additional health care visits that may lead to mothers’ discouragement and decreased confidence. Given the concerns about breastmilk production and newborn weight gain, discharge may be delayed for these families placing additional financial burden on the health care system. Newborn weight loss is the driver
for other interventions and puts at risk women’s decisions to continue breastfeeding. The initiation of breastfeeding could be protected by preventing iatrogenically imposed, exaggerated weight loss.

Newborn weight loss was measured as the lowest weight recorded on the infant’s chart prior to discharge. Therefore, any baby who had > 7% weight loss prior to discharge had this weight considered to be a primary outcome.

For the primary outcome of lowest newborn weight prior to discharge, babies were weighed routinely on the postpartum unit using the Medela BabyWeigh™ scales. In order to ensure the accuracy of this measure, the scales used were designed specifically for weighing infants and were calibrated weekly by the equipment technician for the scales in the Labour and Delivery Unit and by the principal investigator for the scales on the postpartum unit. Secondary outcomes of exclusive breastfeeding and Breastfeeding Clinic appointments made prior to discharge were abstracted from the in-hospital postpartum database. Breastfeeding Self-Efficacy Scale scores were collected by the principal investigator or research nurse by administering the questionnaire to women on the postpartum unit using the BSES-SF tool (Dennis, 2003). Exclusive breastfeeding was considered to have been achieved when only breastmilk was being fed to the infant.

The Breastfeeding Self-Efficacy Scale Short Form (BSES-SF) (Dennis, 2003) was administered prior to discharge (see Appendix F). The BSES-SF is a 14 item tool using a 5-point LIKERT-type scale with scores summed to produce a range from 14 to 70. Higher scores indicate higher levels of breastfeeding confidence. The BSES-SF has established internal consistency (Cronbach’s alpha of 0.97), construct validity and predictive validity (Dennis, 2003). The BSES measures a mother’s confidence in her ability to breastfeed and is predictive of
breastfeeding duration and exclusivity (Dennis, 2003). This tool is a strong measure of breastfeeding self-efficacy and was used to evaluate the effectiveness of conservative fluid management in labour. This was the first trial to evaluate the effect of an intrapartum intervention on BSES scores.

Other outcomes such as NT-proBNP levels and pH were measured by obtaining venous cord blood samples at the time of delivery. The use of NT-proBNP for the purpose of identifying fetal response to IV fluid intrapartum was experimental. NT-proBNP samples, obtained at delivery, were centrifuged when they arrived at the lab and the plasma was separated and frozen. When the study was completed, the samples were assayed in batches. The instrument used to assay the samples was the Elecsys 2010, manufactured by Roche Instruments. The reagents used were ProBNP II, ProBNP CalSet and Cardiac II.

**Implementation and Data Collection**

Prior to the start of the trial, the principal investigator made formal presentations to the members of the Department of Obstetrics and Gynaecology, the Department of Obstetrical Anesthesia and the Department of Family Practice Obstetrics. The presentations introduced the trial, reviewed related literature and explained the intervention and what the physician’s role would be during the trial. Each presentation was met with the support of the physicians who work in the study site’s labour and delivery unit. More informal meetings took place with nursing staff. Education for conservative care nurses is described in the section called Contamination. The trial was promoted by posters in the physicians’ offices and obstetricians distributed a trial information sheet for women at their 36 week visit.
The principal investigator was on call by pager 24 hours a day, seven days a week, for duration of the recruitment period, except for vacation time. Senior nurses who worked in the early labour assessment area became familiar with inclusion and exclusion criteria and how to approach women to determine if they were interested in hearing more about the trial. This was accomplished through individual teaching provided by the principal investigator. When the study was introduced, if the woman was interested in hearing more about the trial, the nurse would page the principal investigator, or as time passed, the nurses had often reviewed the trial and obtained consent by the time they paged the principal investigator. After informed consent was obtained, the principal investigator checked with the charge nurse in the labour and delivery unit to ensure that both a conservative care nurse and a usual care nurse were unassigned. If their availability was confirmed, randomization took place.

The principal investigator then entered the woman’s name and study ID into the trial log and added the patient ID number to the data collection envelope and all the forms inside. The principal investigator confirmed with the nurse assigned to the woman that she understood the elements of the intervention, that she had a copy of the pocket card summarizing the appropriate intervention and that she knew that the principal investigator was always available by pager. Any clarification or teaching that was appropriate was done at that time. The principal investigator checked with the unit at every change of shift, either in person or by phone, to determine if any trial participant had delivered. If trial participants were still in labour, the principal investigator would ensure that the appropriate nurse was assigned to the woman and that the assigned nurse was comfortable with the details of the intervention.

Once a woman had delivered her baby and was transferred to the Mother Baby Unit, the principal investigator would ensure that a coloured sticker, identifying the family as participants
in the FILL Trial, was on the woman’s chart. Participants were identified to the charge nurse and a determination was made of when the 48 hour mark would be reached so that discharge could take place after that time. The principal investigator then spoke to the nurse assigned to the woman so that the nurse could review the timing of discharge.

On the day of discharge, the principal investigator met with the woman to administer the Breastfeeding Self Efficacy questionnaire and confirmed that the nurse assigned to the family was aware the family was participating in the trial and emphasized the need for the newborn’s weight at the time of discharge.

After discharge, the lowest recorded weight was abstracted from the newborn’s chart twice and entered into different fields in the trial database. The second data entry was by a research assistant blinded to group allocation.

Nursing staff at the study site demonstrated an exemplary commitment to the success of the trial. They carefully considered women for eligibility, adjusted their workload to ensure that randomization could take place, contacted the principal investigator when they were unsure about the trial protocol and advocated for the trial’s completion.

**Monitoring Compliance**

Compliance was considered to be achieved if the following measures were met:

1. Preload for epidural analgesia is $< 500$ mls in conservative group and $\geq 500$ mls in the usual care group.

2. Following the first hour after the initiation of epidural analgesia (when the initial IV preload was administered) the infusion rate was $< 125$ mls per hour in the conservative group and $\geq 125$ mls per hour in the usual care group.
Data were collected regarding whether a fluid bolus was given for maternal fever > 38 degrees Celsius. Total fluid intake was obtained from the trial data collection sheet and mean hourly infusion rates were then calculated.

Compliance was monitored for each woman’s care by the principal investigator. Each set of data collection forms was reviewed within 24 hours of delivery for compliance with the study protocol. When a preload volume or hourly rate did not comply with the fluid protocol or if data were missing, the principal investigator reviewed the form with the individual nurse to ensure that the protocol was understood.

**Contamination**

Performance bias was the largest threat to this trial due to the risk of women in the control group receiving the intervention. Contamination effects were addressed by having nurses who were only assigned to women in the conservative care group. There were approximately 75 nurses working in the Labour and Delivery Unit of the participating hospital. All full time and part time nurses were invited to receive preparation to provide the FILL Trial intervention. An email was sent to all nurses in the unit inviting them to volunteer for this role.

Conservative care nurses made up approximately half of the unit staff and received preparation that consisted of a one-on-one education session with the principal investigator. Conservative care nurses were introduced to the trial and the intervention was described in detail. Elements of the intervention, such as more frequent assessments, the trigger volume of >2500 mls requiring review with the physician, conservative IV hourly volume targets and the treatment of fever with acetaminophen, were explained. Conservative care nurses were given a laminated pocket card describing the elements of the intervention. There was an opportunity for
conservative care nurses to become familiar with the data collection sheets and to ask any questions they had about the intervention. All staff who volunteered to become a conservative care nurse received orientation to their role. Approximately 34 nurses initially volunteered. Three staff went on maternity leave during the course of the trial were replaced by new volunteers, nurses who were newly hired to the unit and had not provided usual care.

During the trial, the charge nurse assigned conservative care nurses to care for women who were recruited to the treatment arm of the trial. Usual care nurses were assigned to women randomized to usual care. To ensure that usual care was a distinct treatment protocol, a laminated pocket card was also developed to summarize the lower limits of fluid volume for the usual care nurses. Women were only recruited when both a conservative care nurse and a usual care nurse were available to take a patient assignment.

**Losses to Follow-up**

Women were recruited upon presentation to the early labour assessment area and the trial intervention ended with the birth of the newborn. Minimal losses to follow-up for the primary outcome were expected. This was based on negligible loss to follow-up in trials where the intervention was limited to the intrapartum period (Cheek, Samuels, Miller, Tobin & Gutsche, 1996; Kinsella, Pirlet, Mills, Tuckey & Thomas, 2000; Kubli, Shennan, Seed & O’Sullivan, 2003; Shannon & Ramanathan, 1998; Zamora, Rosaeg, Lindsay & Crossan, 1993). Excluding families desiring discharge prior to 48 hours contributed to the completeness of data.

**Sample Size**

The proportion of infants, born to low risk women who received epidural analgesia and planned to breastfeed, that lose > 7% of their birth weight, was 28% based on a report generated
by the site hospital’s perinatal database summarizing births from 2004 to 2006. Sample size for this trial was based on the ability to detect a reduction in the rate of infants who lose > 7% of their birth weight in the conservative care group, from 28 to 20 percent (a 28% relative reduction). The relative reduction of 28% was an estimate of the impact of fluid overload on weight loss. The total sample size needed to compare a 2 sided test of hypothesis comparing a proportion of 0.28 to 0.2 with 80 percent power (at alpha=0.05) was 184 women, or 92 women per arm. The recruitment target was 100 women per group, inflating the number required to account for possible dropout.

Data Collection and Data Management Procedures

A trial-specific ACCESS database was created to link data from the existing in-house Labour and Delivery and Post Partum Databases that have been in existence since 1994 and 1999 respectively (see Appendix G for the data collection fields exported from the in-house databases). Trial participants’ records in the two in-house databases were linked using the unique mother’s record ID generated by the Labour and Delivery Database that was subsequently captured in the Post Partum Database. The trial-specific database also included the data abstracted from each woman’s and infant’s chart that was entered from the trial data collection forms.

A Trial Screening Form (see Appendix H for all data collection forms) was completed with women interested in hearing more about the trial. If inclusion criteria were met and consent was obtained, the woman was recruited and assigned a sequential FILL Trial ID number. Trial ID numbers were carefully added to the trial data collection packages and double checked to ensure there were no duplicate numbers assigned in error.
Once the woman was randomized, using www.randomize.net, the woman’s name and trial ID number and group allocation were added to a Master Record. The Master Record was stored separately from all other trial data. Electronic enrolment notification including study ID number and date of randomization was received from www.randomize.net and monitored closely. These notifications were saved on a secure server at the hospital.

Different data collection strategies were considered with respect to maximizing data accuracy. Data could have been abstracted from the patient chart by hand and recorded on data entry sheets and then entered into the Access database. This approach would have provided two opportunities for error, once in interpreting the information in the chart and again during data entry. Use of the in-house databases had the advantage of the data being entered by the care providers who best knew the events of the woman’s and newborn’s care.

Disagreement between the Labour and Delivery database and obstetrical patient charts had been formally evaluated by comparing data values in a random sample of 638 charts as part of a quality assurance project conducted several years ago at the site hospital. Overall disagreement was low, with no disagreements as to whether or not it was a multiple birth or a c/section delivery, 0.8% disagreement as to gender, 1.7% disagreement as to birth weight (0.8% disagreement of > 100g), 4.1% disagreement as to whether labour was induced and 0.6% disagreement as to 5 minute Apgar score. The low level of disagreement supported the decision to use the in-house database as a data source.

The FILL Trial database was housed securely on the hospital’s network server, as are the in-house databases. The trial database was designed such that the research nurse could identify study participants from a list of patients in the in-house databases. A computer program then prompted the research nurse for the woman’s Trial ID number, and exported the fields of data
needed for the trial from the in-house databases into the FILL Trial database. A function within
the trial database was designed to enable the research nurse to verify the completeness of data.
Another function identified data values outside predetermined ranges or values that violated
established logic checks. Missing data and data requiring checking were corrected at the time of
data entry.

Weights were recorded onto the infant’s chart by the assigned nurse and then abstracted
onto the data collection form by the principal investigator or research nurse. Abstraction
guidelines were developed to support consistent application of data collection rules. A second
person, blinded to group allocation, abstracted this data as a double check and entered it onto a
separate data collection sheet and then entered into the trial database. The database was created
so that a report could be run to compare the double entry of these outcome data and thus,
discrepancies could be reconciled and accuracy ensured.

A final program to verify data completeness and range and logic checks was run when
data entry was completed. Any data problems identified, including discrepancies between the
duplicate entries of outcome data, were resolved using the patient chart as the gold standard.

Data Analysis

An intention to treat analysis was used in which all women randomized were included in
the analysis. SAS 9.2 software was used for analysis (Cary NC, USA, copyright 2008).
Demographic and baseline variables were analyzed and compared using descriptive statistics
reporting frequencies and percentages. A significance level of p < 0.05 was considered
statistically significant for the primary outcome, the effect of conservative fluid management on
weight loss in the breastfed newborn. Using the Bonferroni correction, a more stringent level of
significance of 0.017 was used for secondary outcomes of Breastfeeding Self-Efficacy Scale scores, exclusive breastfeeding and breastfeeding clinic appointments. Other outcomes have been described descriptively using frequencies.

Statistical methods used depended on the distribution of outcome variables. Where there was normal distribution, dichotomous variables, such as the primary outcome of weight loss >7%, was analyzed using Chi square tests. Continuous variables, such as BSES-SF scores, were analyzed using independent two-sample t tests. As secondary analysis, a descriptive subgroup analysis took place and a logistical regression was conducted on the baseline variable of parity and the outcome of weight loss > 7 % as an exploratory exercise for an interaction effect between treatment group and parity.

Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) was established for this trial. The aim of this committee was to safeguard the interests of trial participants and investigators as well as to assess the safety of the trial’s interventions. The committee members were familiar with the trial and accepted the terms of reference for the committee (see Appendix I). The membership of the committee consisted of three individuals, a neonatologist, a maternal fetal medicine specialist and an expert perinatal nurse. The neonatologist was appointed as chair of the committee. Members were chosen because they were experienced in clinical trials and in the clinical areas of obstetrics and neonatology. The members were independent of the trial and did not have any competing interests in the trial.

The DSMC agreed at the start of the trial to meet to review any maternal or newborn adverse events and report their deliberations to the principal investigator within 2 weeks of
notification of an adverse event. When an adverse event occurred, the principal investigator provided the DSMC chair with all the details of the event. Criteria for reporting included any infant admitted to the NICU for more than 48 hours, any woman admitted to the ICU or any maternal, fetal or neonatal death occurring prior to discharge. Identifiers and the treatment allocation were removed from the information provided. DSMC members agreed that they would not share confidential information with people outside the DSMC, including the principal investigator or other members of the trial team. The chair of the DSMC communicated with the other committee members, collated their responses and drafted reports of the committee’s decisions. Reports regarding adverse events were returned to the principal investigator. Possible recommendations of the DSMC Committee could have been that no action was needed and that the trial could continue as planned or the Committee could recommend early stopping of the trial due to safety concerns.

The DSMC reviewed five adverse newborn events from this trial, all involving admission to the NICU for more than 48 hours, and provided advice on the conduct of the trial to the principal investigator which was shared with the thesis supervisor. In each of the five cases reviewed by the DSMC, the recommendation was that the trial protocol did not contribute to the admission to the Neonatal Intensive Care Unit and that the trial could continue.

Ethics and Human Subjects

Ethical approval was received from the Research Ethics Board at both Sunnybrook Health Sciences Centre, August 21, 2008, and the University of Toronto, September 19, 2008, protocol reference 23292. Informed consent was obtained ensuring women understood what was involved in the trial and that their participation was voluntary and they could withdraw from the
trial at any time (see Appendix J and K for the FILL Trial Information Sheet and Consent Form). Patient confidentiality was maintained by ensuring patient names and trial identification numbers appeared only on the master list that was kept securely and separately from other study forms. Paper forms were kept locked in a filing cabinet in the principal investigator’s office. Computers used to retrieve and enter into the database were password protected and only research staff working on the trial had access to the password linked with the trial database. Computer files were saved on the secure hospital server and were regularly backed up according to hospital policy. The trial was registered through the International Standard Randomized Controlled Trial Register, number 06221064.
Chapter 4

Results

Derivation of the Sample

Recruitment to the trial took place between October 27, 2008 and December 16, 2009. Figure 3 illustrates the flow of participants through the trial. Two hundred and thirteen women consented to participate in the FILL Trial. Two hundred women were in the final sample, 100 in the conservative care group and 100 in the usual care group. Reasons why women who had consented were not randomized included the lack of availability of an unassigned nurse for either the conservative or usual care groups (n=11) and women who had been ambulating who were too far dilated to meet eligibility criteria when they returned to the unit for re-assessment (n=2).

Reasons women declined to participate included an unwillingness to stay for 48 hours post delivery. This was the most common reason given, particularly for multiparous women who wanted to limit their length of stay in order to return home sooner. Other women, or their partners, were concerned about the safety of the trial and some were too preoccupied by labour to consider giving consent. See Appendix L for the recruitment summary.

Compliance

Ensuring compliance to the study protocol was evaluated by determining adherence to the elements of the intervention. Compliance was monitored for each woman’s care by the principal investigator. Compliance was considered to have been achieved if the following measures had been met:
1. Preload for epidural analgesia is <500 ml in conservative group and ≥ 500 ml in the usual care group,

2. The infusion rate is <125 ml per hour in the conservative care group and ≥125 ml per hour in the usual care group.

---

**Figure 3: Flow of Participants Through the FILL Trial**

- **Consented to participate (n=213)**
- **Enrollment**
  - Staff Unavailable (n=11)
  - Not meeting inclusion criteria (n=2)
- **Randomized**
- **Allocation**
  - Allocated to Conservative Care (n=100)
    - Received allocated intervention (n=100)
    - Lost to follow-up (n=0)
    - Analyzed (n=100)
    - Excluded from analysis (n=0)
  - Allocated to Usual Care (n=100)
    - Received allocated intervention (n=100)
    - Lost to follow-up (n=0)
    - Analyzed (n=100)
    - Excluded from analysis (n=0)

---
As well, when a woman in the conservative care group received 2500 mls of IV volume, the nurse had a conversation with the woman’s physician, communicating her fluid status. Fluid boluses for fever were not given as a first line of therapy for women with fever in the conservative care group.

### Table 1 Compliance with the FILL Trial Intervention

<table>
<thead>
<tr>
<th>Compliance Measure</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2500 mls IV fluid administered</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>Acetaminophen given for fever</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Fluid bolus for vomiting</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Fluid bolus given for abnormal FH tracing</td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td>Mean Preload volume (mls) (SD)</td>
<td>326 (165)</td>
<td>608 (157)</td>
</tr>
<tr>
<td>Mean IV volume infused (mls) (SD)</td>
<td>1430 (669)</td>
<td>2477 (1170)</td>
</tr>
</tbody>
</table>

Compliance to group allocation was excellent. Nurses quickly recognized the importance of ensuring that only a conservative care nurse cared for a woman assigned to conservative care, and that only usual care nurses were assigned to women randomized to the usual care protocol. This compliance was confirmed by the principal investigator at every shift change during the recruitment period, either in person or by telephone. Nurses often took on additional work load to ensure compliance to group allocation. For example, a nurse may just have finished caring for a patient while another nurse may not have had a previous assignment when a woman was randomized and needed to be assigned to the busier nurse.

A summary of compliance with the FILL Trial intervention is found in Table 1. There were few episodes of non-compliance. For example, four women received preload volumes in
the conservative care group > 500 mls. Three of these episodes related to the preferred practice of an individual anesthetist of infusing one liter of fluid prior to epidural administration. Once this contributor to non-compliance was identified, recruitment no longer took place when the individual anesthetist was on call.

There were ten instances where the expected volume of fluid bolus for epidural administration in the usual care group was < 500 mls. In some instances this happened because a woman’s labour progressed so quickly that there was not time to administer the bolus or, in one case, to initiate the epidural prior to delivery. In other situations, the availability of the anesthetist to administer the epidural determined how much of the expected preload was received. The differences between the mean volumes infused between groups for preload and total volumes indicate good compliance with the study protocol aimed at the administration of less intravenous fluid to women in the conservative care group.

Average hourly IV infusion rates between groups were calculated by using the formula 

\[
\frac{\text{mean volume of IV fluid infused} - \text{mean preload volume}}{\text{mean length of IV infusion in minutes}} \times 60\text{ minutes}
\]

The average hourly rate of IV infusion for the conservative care group was 110 mls per hour, while the average rate for the usual care group was 200 mls per hour. This difference indicates compliance to the conservative and usual care protocols.

Reaching a ‘trigger volume” of 2500 mls was identified as an event that would require the conservative care nurse to communicate this information with one of the woman’s physicians. All situations were documented as having been communicated.

Similar numbers of women in each group received acetaminophen for intrapartum fever, 5% and 6% respectively for conservative and usual care groups. Acetaminophen was used as a first level approach for five women in the conservative care group and as a second level
approach for six women in the usual care group, after the administration of fluid boluses had not resulted in temperature regulation. Fewer women in the conservative care group were given fluid bolus for abnormal tracings, compared to the usual care group.

Baseline Characteristics of Participants

Table 2: Baseline Characteristics of FILL Trial Participants

<table>
<thead>
<tr>
<th></th>
<th>Conservative Care (n= 100)</th>
<th>Usual Care (n= 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>Maternal Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-35</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>&gt;35</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Gestational Age 37-41 weeks</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Primiparous</td>
<td>79</td>
<td>72</td>
</tr>
<tr>
<td>Previous Live Births</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Previous Breastfeeding Experience</td>
<td>17* (18%)</td>
<td>22* (23%)</td>
</tr>
</tbody>
</table>

*9 missing values, 4 in the conservative care group and 5 in the usual care group

Table 2 summarizes the baseline characteristics of participants in the FILL Trial.

The mean age of women participating in the trial was 33.5 (±4.48) years. One hundred and twenty women (60%) were between 20 and 35 years of age, 80 women (40%) were over 35 years of age. The majority of women were primiparous, (n=151, 75%). Of the 49 multiparous women, all had a history of previous live births and 39 had previously breastfed. Groups appeared similar with respect to these characteristics.
Labour Events

Table 3 summarizes labour events for conservative and usual care groups. While caesarean section rates were similar for both groups, there were more instrumental deliveries in the conservative care group (27 versus 13) and thus fewer spontaneous deliveries in the conservative care group. Appendix M summarizes reasons for vacuum and forceps deliveries.

Table 3: Comparison of Labour Events in Conservative and Usual Care Groups

<table>
<thead>
<tr>
<th>Labour Event</th>
<th>Conservative Care (n= 100)</th>
<th>Usual Care (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Vaginal Delivery</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>Vacuum</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Forceps</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Caesarean Section</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Oxytocin administered</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Received IV bolus for fever</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

The mean duration of time from admission to delivery was 637 (±322) minutes in the conservative care group and 651 (± 345) minutes in the usual care group. The mean length of time from the initiation of the intravenous infusion to delivery was 573 (±275) minutes for the conservative care group and 594 (±299) minutes for the usual care group.

Primary Research Question

For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for fluid management versus usual care on breastfed newborns’ weight loss > 7% prior to discharge?
Complete data were obtained for the primary outcome of lowest recorded newborn weight prior to discharge, as well as other outcomes. Weight loss across the entire sample was 6.85% (±2.11), representing a mean weight loss of 237 (±85) grams. Mean weight loss in the conservative care group was 6.69% (± 2.07) and 7.00% (± 2.12) in the usual care group. Forty four babies in the conservative care group lost more than 7% of their birth weight prior to discharge. In the usual care group, 48 babies lost more than 7% of their birth weight. Table 4 summarizes this outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n= 100 )</th>
<th>RR (95% CI)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &gt; 7%</td>
<td>n=44</td>
<td>n=48</td>
<td>0.92</td>
<td>0.32</td>
<td>0.57</td>
</tr>
</tbody>
</table>

**Secondary Research Question**

*For low risk women receiving epidural analgesia in labour, what is the effect of conservative fluid management versus usual care on: breastfeeding self-efficacy, breastfeeding clinic visits and the incidence of exclusive breastfeeding?*

The mean Breastfeeding Self Efficacy Score (BSES) for the conservative care group was 49.70 (±9.03) and for the usual care group was 49.85 (±11.75) out of a possible score of 70. Other breastfeeding outcomes are summarized in Table 5.
Table 5: Breastfeeding Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n=100)</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding Clinic Visits</td>
<td>31</td>
<td>40</td>
<td>1.77</td>
<td>0.18</td>
</tr>
<tr>
<td>Exclusive Breastfeeding at time of BSES</td>
<td>67</td>
<td>66</td>
<td>0.21</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Other Research Questions

*For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for fluid management versus usual care on: venous cord blood NT-proBNP levels, venous cord blood pH values < 7.25, 5 minute Apgars >7, delayed discharge and admission to the Neonatal Intensive Care Unit?*

Table 6 summarizes NT-proBNP levels for the conservative and usual care groups.

Table 6: NT-proBNP levels in the Conservative and Usual Care Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NT-proBNP 25th, 75th. p/mol</td>
<td>699 (484,1063)</td>
<td>574 (442,915)</td>
</tr>
</tbody>
</table>

Similar numbers of babies in each group had venous cord blood pH levels of less than 2.5. All but one baby had five minute Apgar scores >7. Fifteen babies in the conservative care group had their discharge delayed, while 16 babies in the usual care group were delayed. Twenty-two infants were admitted to the NICU at the time of delivery, 15 in the conservative
care group and 7 in the usual care group. Table 7 summarizes these measures of newborn well-being.

**Table 7: Measures of Newborn Well-being**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH &lt; 7.25</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>5 min Apgar &gt; 7</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Infant discharge delayed</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

A summary of reasons for admission to the NICU can be found in Table 8. Eight percent of women in the conservative care group had fever > 38 degrees Celsius compared to the incidence of fever in the usual care group of 6%. Since there were more babies in the conservative care group admitted to the NICU for a septic work-up, these babies’ hospital charts were reviewed to determine the reasons for this assessment. A chart review indicated that most women developed fever at the last or second last assessment before delivery.

**Table 8: Reasons for NICU Admission**

<table>
<thead>
<tr>
<th>Reason for NICU Admission</th>
<th>Conservative Care (n=100)</th>
<th>Usual Care (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic workup for maternal fever &gt; 38 Celsius</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Septic work other reasons</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Assessment</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Septic work-ups with positive lab results</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Of the ten conservative care babies having septic work-ups, eight were because the mother had an intrapartum fever > 38 degrees Celsius. Of these eight febrile women, three were
Group B Strep positive and one had prolonged rupture of membranes. There were no additional risk factors identified that would predispose the other four mothers to intrapartum fever. For the two babies born to afebrile women in the conservative care group who had septic work-ups in the NICU, one mother was Group B Strep positive and one had prolonged rupture of membranes.

While 6 women in the usual care arm of the trial received IV fluid bolus for intrapartum fever, one baby was admitted to the NICU due to maternal fever. Three of the babies born to these 6 women did have intrapartum fevers but for some reason their infants were not admitted to the NICU for septic work-ups. Of the other two babies in the usual care arm of the trial requiring septic work-ups, there was one woman who was Group B Strep positive and one baby who experienced respiratory distress in the immediate neonatal period.

All septic work-up results for babies in both groups were negative for infection. Across both treatment groups, there was no difference in the amount of fluid given to women whose babies were admitted to NICU and women whose babies who were not admitted to the NICU, 2124 (±923) mls versus 1932 (±1105) mls.

**Safety Monitoring**

The Data Safety Monitoring Committee (DSMC) reviewed five cases of infants admitted to the NICU for more than 48 hours during the course of the trial. Of the five infants, two had meconium noted upon rupture of membranes. Four infants were admitted directly to the NICU with respiratory difficulties, one was admitted at 67 hours of age due to symptomatic hypoglycemia. Three infants experienced transient tachypnea of the newborn and one had a pneumothorax. In each case, the Data Safety Monitoring Committee concluded that involvement in the trial did not predispose the infant to any additional risk and recommended that the trial continue as planned.
Exploratory Analyses

To examine potential factors related to weight loss, an exploratory regression analysis was performed. Parity was identified as the sole putative predictor known prior to randomization that might affect weight loss. Therefore, a linear regression was performed regressing percentage of weight loss on intervention group, parity and the interaction of the two. When the interaction terms involving the conservative care group and parity were entered into the model, the \( p \) value did not reach statistical significance, suggesting that any effects of parity on percentage weight loss did not depend on intervention group. A summary of the modeling exercise is found in Table 9.

Table 9: Percentage of Weight Loss as a Function of Parity and Intervention Group

<table>
<thead>
<tr>
<th>Explanatory Baseline Variable</th>
<th>Beta Coefficients (n=200)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td>0.85</td>
<td>0.07</td>
</tr>
<tr>
<td>Interaction between treatment &amp; parity</td>
<td>0.68</td>
<td>0.37</td>
</tr>
<tr>
<td>Intervention</td>
<td>-0.85</td>
<td>0.15</td>
</tr>
<tr>
<td>Intercept</td>
<td>6.40</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Further analysis was conducted to look at the subset of the sample of weight loss in babies whose mothers received > 2500 mls of IV fluid intrapartum. For this group of 51 infants, their weight loss was significantly different from the infants whose mothers received less fluid, 7.4% versus 6.6%, \( t=2.20, p=0.03 \). As well, there was a significantly higher mean volume of fluid infused to the mothers whose 16 infants lost > 10% of their birth weight, 2534 mls versus 1903 mls, \( t=2.25, p=0.03 \). Twice as many infants in the usual care group lost more than 10% of their birth weight compared to infants in the conservative care group, 11 infants versus 5.
Supplementation is a potential co-intervention in the FILL Trial, since 33 babies in the Conservative Care group and 34 babies in the Usual Care group were supplemented with formula prior to discharge. It is not known how much formula individual babies were given, just that they had received this alternative food source. However, there was not a significant difference in weight loss between the group of babies supplemented versus those that were exclusively breastfed, 6.80% (± 1.78) and 7.03% (±2.67), \( p=0.53 \). Considering the subset of infants exclusively breastfed in both usual and conservative care groups, there was no difference in weight loss between study groups, 6.85% (± 1.80) and 6.74% (± 1.77), \( p=0.71 \).

There was not a difference between groups in the number of women who had caesarean deliveries, but twice as many babies in the conservative care group were delivered by vacuum and forceps compared to the usual care group. Women who had instrumental deliveries had longer lengths of time of IV infusion than women who delivered spontaneously or who had caesarean section, 677 (±320) minutes versus 561 (± 274) minutes, \( p < 0.02 \). There was no difference in the IV fluid volumes received between women having instrumental deliveries 1924 mls (±1012), and women having spontaneous or cesarean deliveries 1960 mls (±1106), \( p=0.85 \).
Chapter Five
Discussion

This chapter focuses on a description of the methodological strengths and limitations of the trial, a critique of the study’s conceptual framework and a review of the results in light of available evidence.

The primary outcome of interest in the FILL Trial was the proportion of breastfed infants who lost > 7% of their birth weight prior to discharge. Forty-four infants in the conservative care group and 48 infants in the usual care group lost > 7% of their birth weight, resulting in a non-statistically significant difference between groups.

There were no statistically significant differences between groups for breastfeeding exclusivity, breastfeeding clinic appointments or Breastfeeding Self Efficacy scores. More babies in the conservative care group required initial admission to the NICU, most often for septic work-up for maternal intrapartum fever. No septic work-ups yielded positive results. There were more instrumental vaginal deliveries in the conservative care group. A hypothesis generating exercise did not identify significant variables affecting percentage weight loss. However, in the subgroup of women who received > 2500 mls of IV fluid during their labour, the infants born to those women lost more weight than infants whose mothers received < 2500 mls.

Strengths and Limitations

This randomized trial was strengthened by having an interdisciplinary group develop a clinical practice guideline for fluid management, using an objective primary outcome measure,
achieving excellent compliance, controlling for various sources of bias and developing a trial specific database to ensure accurate data entry.

An interdisciplinary group, consisting of a staff nurse, a nephrologist, a maternal-fetal medicine specialist, an anesthetist, a generalist obstetrician and the principal investigator, developed the conservative care intervention following a systematic review of the literature and the development of a clinical practice guideline for managing IV fluid in low risk labour. This process ensured that there was an evidence based approach to the elements of the intervention.

The primary outcome, weight loss > 7% prior to discharge, came from the recommendations of the International Lactation Consultants’ Association (1999) and the Academy of Breastfeeding Medicine (2007). Both groups have identified 7% weight loss as a marker of unsuccessful breastfeeding initiation. Weight loss is an objective measure, not under the influence of the nurse who delivered the IV fluid intrapartum or the physician who provided obstetrical care. To ensure accuracy of the measure, the newborn scales were calibrated weekly during data collection. The primary outcome was validated through blinded, double entry of the lowest recorded infant weight to ensure accuracy.

Compliance with the intervention was very good with conservative care nurses being carefully assigned to women in the treatment group. There were statistically significant differences in the volumes of preload administered and the total volume infused between groups, indicating that nurses followed the study protocol for both group allocations. It can be concluded that performance bias was avoided.

Selection bias was not an issue for this trial since randomization was centrally controlled and concealed by using a web-based tool. Entry criteria were captured for each consenting woman and the website [www.randomize.net](http://www.randomize.net) determined group allocation. Since not a single
participant was lost to follow up and there are complete data for the primary outcome for all 200 participants, attrition bias is not a concern for the trial. While caregivers and women were not, and could not be, unaware of group allocation, the persons collecting and entering data for the second value of lowest weight during hospitalization were blinded to group allocation.

A strength of the trial was the development of a trial-specific database to enter and manage data. The trial specific database was linked with the hospital’s intrapartum and postpartum ACCESS databases, enabling fields of data to be exported from the existing databases. This approach minimized data entry error. The trial database had logic checks for outcomes such as ensuring intrapartum and postpartum databases were completed and sealed before trial data could be entered, checking that the date and time of admission did not occur before date and time of the epidural administration, as well as setting range limits on gestational age, birth weight, Apgar scores and blood work levels. These data entry steps contributed to data accuracy.

The results of this trial are generalizable to breastfed babies born to women experiencing low risk pregnancies, who received epidural analgesia during labour, were well hydrated at the initiation of labour and did not have a history of breast surgery.

One limitation of the trial was that there was a potential co-intervention, since about a third of babies in the Conservative Care group and the Usual Care group was supplemented with formula prior to discharge. It is not known how much formula individual babies were given, just that they had received additional food. This difference in volume may have affected newborn weight loss and subsequently, the outcome of the trial. The potential for this co-intervention should have been anticipated and a plan created to track volume and exact timing of supplementation.
Conceptual Framework

The conceptual framework for this trial was based on the physiology of fluid management, highlighting the relationship between fluid overload, maternal-fetal circulation and early newborn weight loss in breastfed infants. Water and electrolytes move between intracellular and extracellular spaces. When more IV fluid than needed is infused, there is a decrease in colloid osmotic pressure and subsequent movement of intravascular fluid into the extravascular space. This results in edema and fluid retention. This conceptual model supported the hypothesis that conservative fluid would prevent the expansion of the extravascular space, avoiding fluid overload in the laboring woman and subsequently in her infant and subsequent newborn weight loss. It was hypothesized, as well, that conservative volumes of fluid administered to the laboring woman would maintain normal NT-proBNP levels in cord blood, decrease admissions to the NICU, result in higher breastfeeding self efficacy and contribute to improved breastfeeding exclusivity.

Walsh and Walsh (2005) defined fluid overload as intravenous fluid associated with morbidity, including the development of tachypnea, tachycardia, hypoxia, pulmonary crepitations, pulmonary congestion on chest x-ray and the development of gross peripheral edema. When this trial was conceptualized, fluid overload was not well defined in terms of measureable signs and symptoms and therefore it cannot be concluded that the usual care group was overloaded with fluid. The conceptual framework was physiologically sound but was limited in a situation where two volumes of fluid were administered, neither of which created a situation of overload. The conceptual framework could have been strengthened by operationalizing the term ‘overload’ in physiologic terms to allow for its identification.
Review of the FILL Trial Findings

Primary Research Question

For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for fluid management versus usual care on breastfed newborns’ weight loss > 7% prior to discharge?

The overall number of infants who lost more than 7% of their birth weight was 46%. There was no difference in weight loss between conservative care and usual care groups. Average percentage weight loss for all newborns in the FILL Trial was 6.8% (± 2.11). This pattern of weight loss was similar to the 5.8% (±3.2) mean weight loss reported by Maisels et al. (1983) and 6.6% median weight loss reported by MacDonald et al. (2003).

Weight loss for exclusively breastfed infants in the FILL Trial was 6.80% (±1.78) and 7.03% (±2.67) for infants supplemented with formula. Martens (2007) identified factors associated with weight loss for breastfed and formula fed newborns. Mean weight loss for exclusively breastfeeding newborns in Marten’s study was 5.49% (± 2.60). Weight loss for partially breastfed infants in Marten’s group was 5.52% (± 3.02). Given that weight loss > 7% is used as a marker of concern for breastfeeding initiation (Academy of Breastfeeding Medicine, 2007; International Lactation Consultants Association, 1999) it is questionable whether this is a useful guide. If almost half of the infants lose between 6-7% as reported by other studies and this trial, it is suggested that it is not reasonable that such a large percentage of infants are considered to have breastfeeding difficulties based on weight loss.

A recent study conducted to determine the relationship between intrapartum maternal fluids and neonatal weight loss used a convenience sample of 200 women whose infants were both breast and formula fed (Lamp & Mackie; 2009). Mean volumes of fluid intake (both IV
and oral) ranged from 2522 ml (±933) for unmedicated vaginal births to 5014 ml (±1912) for unscheduled caesarean sections. Mean weight loss for all babies at 48 hours was 5.2% (±2.0), 6.7% (±2.03) for exclusively breastfed infants and 6.6% (±2.27) for supplemented breastfed infants. The multivariate analysis conducted for this study did not identify a relationship between maternal intrapartum fluid intake and neonatal weight loss.

In Martin’s (2007) study, for the entire sample, where 50% of infants were exclusively breastfed, 2.46% of infants lost > 10% of their birth weight. In Wright and Parkinson’s (2004) cohort study of 961 term infants, where 51% of infants were breastfed, 3% lost > 10%. Whereas, 8% of infants, exclusively and partially breastfed in the FILL Trial lost more than 10% of their birth weight. This difference could be due to the fact that not all infants in the other studies were breastfed or were born to women with epidural analgesia and intravenous therapy.

The population of infants losing > 10% is one of interest. The infants who lost more than 10% of their birth weight were born to mothers who received a significantly higher mean volume of fluid. In the FILL Trial, five infants in the conservative care group and 11 infants in the usual care group lost > 10% of their birth weight, suggesting a possible link between greater weight loss in the usual care group at higher levels of IV fluid infused. For the 51 infants whose mothers received > 2500mls of IV fluid, their weight loss was significantly higher than other infants. This is an area worthy of further exploration. While there was not a difference in weight loss between conservative care and usual care groups, there may be a threshold of fluid volume infused, above which there is a difference in weight loss. It is not yet clear when fluid administered creates fluid balance and when fluid overload occurs.

Intravenous fluid has been hypothesized to be linked to weight loss (Dahlenburg, 1980; Dewey, 2003; Martens & Romphf; ; Tarnow-Mordi, et al., 1981). By suggesting the possibility
of a threshold volume, the FILL Trial challenges the thinking that any IV leads to increased weight loss suggesting that it is the volume of fluid infused that may be the factor. There may be a critical threshold for fluid volume, above which, newborn weight loss is affected.

The lack of effect of a conservative fluid protocol on newborn weight loss was reviewed with staff from the unit where the trial took place. The staff, who are now in advanced practice roles, were surprised to learn that the mean ‘usual’ volume infused was 2500mls. They described routinely infusing four to five liters of fluid to laboring women. Mean fluid volumes reported in Lamp and Mackie’s (2009) study of both IV and oral intake and IV volumes reported by Tranmer (1999), in her trial evaluating the effects of oral intake during labour, averaged more than 3 liters, a higher volume than administered to the usual care group in the FILL Trial.

It is possible that the Hawthorne effect (Jones, 1992) was a factor in this trial and that what was usual care for the trial was not typical fluid management at all. The Hawthorne effect refers to human behavior studies in the 1920s and 1930s that took place at the Hawthorne Works factory. These studies examined how work on an assembly line affected productivity. The results of those famous tests are known as the Hawthorne Effect and refer to alterations in a subject’s behavior due to their participation in the experiment and their awareness that they were being studied.

All staff in the unit where the trial took place knew about the trial and that the intervention was to give less fluid to women in labour. This may have resulted in an alteration in usual care. Even though the volumes between conservative and usual care groups were statistically different, the introduction of the trial may have resulted in a reduction of the volumes administered to the usual care group. It is possible that women in the usual care group and their
babies were not overloaded and it would appear that the outcome of weight loss > 7% is not a proxy for overload.

The lack of effect of the conservative care intervention may be attributed to the lack of clinically significant difference in fluid volume infused between groups, as well as unknown patterns and volumes of supplementation for 30% of newborns. It is concerning that a third of newborns in both arms of the trial were supplemented prior to discharge. Larger volumes of supplementation may have prevented weight loss in some infants. As well, a 7% weight loss may have been too small a percentage to use as the primary outcome. It is possible that 10% weight loss would have been a more clinically relevant outcome since infants who lose more than 10% of their birth weight are considered not simply to have trouble breastfeeding but to be potentially medically unstable.

Sample size was calculated using the incidence of low risk breastfed infants losing > 7% as 28%, a figure derived from the hospital’s in-house database. It was hypothesized that conservative care would have a moderate effect and decrease the proportion of infants losing >7% by 28%. This may have been too large an estimated effect size and therefore, the sample was too small to determine the impact of conservative fluid volumes on breastfed infant weight loss, if weight loss does not occur until higher volumes are infused.

Interestingly, the results of the FILL Trial contradict other intrapartum fluid trials’ findings. Eslamian (2006) conducted a randomized, double blinded trial with 300 primiparous women who received intrapartum IV fluid at either 125 ml per hour or 250 ml per hour. The group that received fluid at a rate of 250 ml/hour had a significantly shorter labour 253 (±97) minutes versus 386 (± 110) minutes, \( p=0.0001 \), and received significantly less oxytocin, 8.1% versus 20.4%, \( p=0.001 \). Eslamian reported a non significant trend towards an increase in
caesarean section rates in the 125 mls per hour group. The difference between groups in mean total volumes of IV fluid infused was 810 mls versus 1065 mls. This equates to a mean difference of 255 mls between groups, suggesting that even small differences in fluid volumes can impact outcomes.

Garite (2000) evaluated the same intrapartum intervention as Eslamian (2006), 125 mls per hour versus 250 mls per hour, with 195 women and reported similar results. These included fewer labours lasting greater than 12 hours, 26% versus 13%, \( p=0.047 \), a non significant trend towards decreased oxytocin use, 49% versus 65%, \( p=0.06 \), and caesarean section rates (10 versus 16) in the 250 mls per hour group. The difference between groups in mean total volume of IV fluid infused was 2008 mls versus 2483 mls. This equates to a mean difference of 475 mls between groups, approximately half the mean difference between groups for the FILL Trial. The works by Garite (2000) and Eslamian (2006) are often cited as evidence that more intrapartum fluid is better, yet it is difficult to conceive of a physiologic basis for such small volumes of fluid affecting labour length and the need for uterine stimulating drugs.

In contrast, in the Fill Trial women in the conservative care group received IV fluid at the rate of approximately 110 mls per hour and women in the usual care group received IV fluid at the rate of about 200 mls per hour, yet there was no difference between groups in the time from initiation of IV fluid administration and delivery, 573 (± 275) minutes versus 594 (± 298) minutes. There was also no difference between groups in caesarean section rate (21% versus 22%) or the use of oxytocin (30% versus 26%). However, there were more spontaneous vaginal births in the usual care arm of the FILL Trial. The difference between groups in mean total volume of IV fluid infused was 1430 (± 669) mls in the conservative care group versus 2477 (± 1170) mls in the usual care group. This equates to a mean difference of 1047 mls between...
groups, a larger difference than seen in the other two trials. It is not clear why the FILL Trial findings differ from those of Garite (2000) and Eslamian (2006).

**Secondary Research Question**

*For low risk women receiving epidural analgesia in labour, what is the effect of conservative fluid management versus usual care on: breastfeeding self-efficacy, breastfeeding clinic visits and the incidence of exclusive breastfeeding?*

This was the first time the Breastfeeding Self Efficacy Scale was used as an outcome measure in a clinical trial to evaluate the effect of an intrapartum intervention on BSES scores. BSES scores were not different between conservative and usual care groups 49.70 (±9.03) and 49.85 (±11.75). Mean BSES scores in the FILL Trial were similar to those reported by Kingston, Dennis & Sword (2007) of 48.8 (±10.69). Breastfeeding Clinic visits and breastfeeding exclusivity did not differ between conservative care and usual care groups. The absence of apparent effect on breast feeding outcomes may be explained by the lack of impact of the intervention on the number of babies with weight loss > 7%.

**Other Research Questions**

*For low risk women receiving epidural analgesia in labour, what is the effect of a conservative protocol for fluid management versus usual care on: venous cord blood NT-proBNP levels, venous cord blood pH values < 7.25, 5 minute Apgar scores >7, admission to the Neonatal Intensive Care Unit and delayed discharge?*

There was an increased number of infants in the conservative care group that were transferred to the NICU for septic work-ups related to maternal fever. Three of these infants
were born to mothers who were Group B Strep positive and one woman had prolonged rupture of membranes. There were also four women who had fever for whom there were no other identifiable risk factors. Eight percent of women in the conservative care group had fever > 38 degrees Celsius compared to the incidence of fever in the usual care group of 3%. Of these three, febrile women in the usual care group, only one infant was admitted to the NICU for a septic work-up. The reason for the difference in the incidence of septic work-ups between groups is not known. The incidence of maternal fever reported in the literature ranged from 5% to 26% with sample sizes ranging from 92 to 1200 women (Lieberman, Lang, Frigolette, Richardson, Ringer & Cohen., 1997; Mantha, Vallejo, Ramesh, Phelps & Ramanathan, 2008; Philip, Alexander, Sharma, Shiv, Leveno, McIntyre & Wiley, 1999).

A chart review of febrile women in the FILL Trial indicated that most women developed fever at the last or second last assessment before delivery. This late onset of fever is a phenomenon reported by Philip et al. (1999). The finding that there was no difference in the mean volume of fluid delivered to mothers of babies admitted to the NICU and those mothers of babies not admitted calls into question the relationship between fluid volume, maternal fever and subsequent NICU admission. The difference in maternal fever between groups could have occurred by chance, but further study is needed.

The mechanism by which epidural analgesia is related to maternal fever is not certain but is thought to be related to changes in thermoregulation following regional analgesia rather than dehydration or infection. Lieberman et al. (1997) evaluated the impact of epidural analgesia on maternal fever in a sample of over 1200 women and reported an odds ratio of 14.5 [95% CI 6.3, 33.2]. Philip et al. (1999) reported that epidural analgesia was independently associated with maternal fever in a sample of over 700 women, OR= 4.0 [95% CI 2.0-7.7]. Primiparity and
prolonged labours greater than 12 hours were also associated with fever, OR=4.1 [95% CI 1.8-9.1] and OR=5.4 [95% CI 2.9-9.9] respectively (Philip et al., 1999). In the FILL Trial, mothers born to babies who were admitted to the NICU had longer lengths of IV infusion than mothers whose infants were not admitted, 714 (± 273.5) minutes versus 568 (± 284.9) minutes, representing a difference of over 2 hours.

Lieberman et al. (1997) concluded that the vast majority of episodes of maternal fever were related to epidural analgesia. So, while more septic work-ups were conducted on babies whose mothers were in the conservative care group, the reasons for this may be multifactoral. Given the recognized role of fever for women receiving epidural analgesia, the differences in septic work-ups between groups could have been a chance finding, inviting further research in this area.

NT-proBNP levels were measured in samples of venous cord blood to determine if there were elevated levels in the usual care group, indicating possible fluid overload. Reference values of venous cord blood samples for NT-proBNP were established by Schwachtgen et al. (2005). Values were measured in pp/mg and ranged from 281-2595 pg/ml (33.16 to 306.21 pp/mol), with a mean value of 818 pg/ml (96.52 pp/mol). The median value of NT-proBNP for infants whose mothers were in the conservative care group was 699 pp/mol (5th, 95th % iles 274, 1578). Women in the usual care group received, on average, one additional liter of fluid compared to women in the conservative care group yet, the median NT-proBNP value for the venous cord blood of babies born to women in the usual care group was lower than the conservative care group (574 pp/mol, 5th, 95th % iles 238, 1552). NT-proBNP values for samples analyzed in the FILL Trial were six to seven times higher than reference values reported by Schwachtgen et al. Nothing is known about the fluid administered to women in Schwachtgen et al.’s study and
reasons for these differences in laboratory values are not known. The fluid volume difference between conservative and usual care groups did not impact fetal NT-proBNP.

There was not a difference between groups in the number of women who had caesarean deliveries, but twice as many babies in the conservative care group were delivered by vacuum and forceps compared to the usual care group. It needs to be considered that receiving less fluid intrapartum could result in fatigue and possible dehydration, leading to the need to intervene during second stage with instrumentation. However, there was no difference in the volume of fluid infused between babies delivered by forceps and vacuum, 1924 mls (±1012) and those delivered spontaneously, 1960 mls (±1106). This lack of difference calls into question the effect of the IV fluid intrapartum on instrumental delivery. Women who had instrumental deliveries had longer lengths of time of IV infusion than women who delivered spontaneously or who had caesarean section, 677 (±320) minutes versus 561 (±274) minutes, but no difference in the IV fluid volumes received.

It is possible that longer labours could result in fatigue, complicated by dehydration for women receiving too little fluid intrapartum, but this does not seem to be an explanation for the differences in the number of instrumental deliveries in this trial. The possibility of performance bias should also be considered, if physicians, delivering women participating in the conservative care group, opted to intervene earlier due to bias that these women were potentially dehydrated. Since instrumental delivery was not a prespecified outcome, it is not possible to explain this finding. The reasons for this difference between groups is likely to be multifactorial, however, given the increased morbidity associated with instrumental delivery, this warrants further study.
Logistic Regression Results

The linear regression performed regressing percentage of weight loss on intervention group, parity and the interaction of the two found that conservative care did not impact these weight loss in babies born to primiparous and multiparous women differently. Martens (2007) identified factors associated with weight loss for breastfed and formula fed term infants born to women with and without epidural analgesia. Factors affecting weight loss included higher birth weight, female sex, epidural use and longer hospital stay. Similar to the FILL Trial, Martens did not find that parity was a significant factor related to newborn weight loss.
Chapter Six

Summary, Implications for Practice and Research, Conclusions

Summary

There is uncertainty regarding how much intravenous fluid should be given during the intrapartum period to women who have epidural analgesia. There are no published protocols or guidelines available to address fluid management in labour to optimize care for women and their infants. The absence of an evidence-based approach to intrapartum fluid management may result in fluid overload, with consequent maternal and newborn morbidity.

The FILL Trial is unique in its contribution to what is known about the effects of intrapartum fluid administration. Several authors have proposed a relationship between IV therapy and newborn weight loss. This is the first trial to evaluate newborn outcomes with two different fluid protocols. The primary outcome of interest in the FILL Trial was the proportion of breastfed infants who lost > 7% of their birth weight prior to discharge.

The FILL Trial was a single site randomized controlled trial comparing a conservative protocol of fluid management with usual care for low risk women receiving epidural analgesia in labour and was the first trial to look at newborn effects of intrapartum fluid administration. The conceptual framework for this trial focused on the physiology of fluid balance and the effects of fluid overload.

Groups were considered similar at randomization and an intention to treat analysis was used. Women in the conservative care group received an IV volume prior to epidural analgesia initiation of < 500 mls and an IV infusion rate of 110 mls per hour. Women in the usual care group received an IV volume prior to epidural analgesia initiation of ≥ 500 mls and an IV infusion rate of 200 mls per hour. Two hundred women participated in the trial, 100 in the
The Fill Trial

conservative care group and 100 in the usual care group. Complete data was available for the primary outcome. Forty-four infants in the conservative care group and 48 infants in the usual care group lost > 7% of their birth weight, $p=0.57$. There were no statistically significant differences between groups for breastfeeding outcomes, including breastfeeding exclusivity or breastfeeding clinic appointments. There were no differences in measures of newborn well being, including Apgar scores, cord pH values, NT-proBNP cord blood levels, delayed discharge or admission to the NICU. A hypothesis generating exercise did not identify significant variables affecting percentage weight loss.

Two outcomes for which differences were not hypothesized prior to the study, instrumental deliveries and NICU admissions, were higher in the conservative care group, pointing to the need for additional research examining the impact of intrapartum fluid volume on method of birth and newborn well-being. The apparent differences in maternal fever requiring NICU admission needs further research as well.

No change in current practice is warranted for intrapartum IV fluid volumes < 2500 mls during labours of healthy women who have epidural analgesia. Future research should focus on the creation of more evidence regarding safe volumes of intravenous fluid during labour.

**Implications for Research**

Further research related to outcomes of intrapartum IV fluid infusion is recommended to build on the evidence of the FILL Trial.

Although the current trial was not powered to detect this effect, it is possible that there is a threshold for IV fluid volume in low risk labours when they receive > 2500 mls that impacts newborn weight loss. More research is needed to identify and confirm this threshold. While it
would be unethical to design a trial that intentionally over hydrates laboring women, a retrospective review, examining outcomes for women and their infants when larger volumes of fluid are infused during labour, could begin to clarify this phenomenon.

A replication of this study using a primary outcome of 10% weight loss, rather than 7% may be a more clinically relevant outcome for a future trial. Babies who lost more than 10% of their birth weight were born to women who received higher volumes of IV fluid, suggesting a link between greater weight loss and higher IV volumes. This is an area worthy of further exploration. While there was not a difference in weight loss between conservative and usual care groups, there may be differences when larger volumes of IV fluid are infused. A threshold may exist above which newborns’ weight loss increases. This is an area worthy of further exploration.

A focus on maternal outcomes related to the safety of fluid volumes would support the identification of a threshold. Such outcomes could include postpartum measures of maternal well-being, including inatrogenic edema and pulmonary function. Women may experience shortness of breath postpartum related to pulmonary edema that is believed to be related to higher volumes of IV fluid infused intrapartum (personal communication WS Chan, March, 2007). Identifying normal pulmonary function postpartum could lead to the confirmation of the relationship of IV intrapartum fluid and pulmonary symptoms and future trials evaluating IV fluid protocols that could prevent this adverse outcome.

While edema is an expected event when too much fluid is given, it was not used as an outcome for this trial since validated, objective measures for edema do not exist. Developing better tools to measure edema could be a future focus of work related to outcomes for fluid administration in labour.
Women with ‘at risk’ or complicated pregnancies such as women with pregnancy induced hypertension or twin pregnancies are believed to experience more fluid overload and subsequent pulmonary edema than low risk births (Samol & Lambers, 2005; Tihtonen, 2007). Thus, research to determine safe volumes for women experiencing these risk factors is needed. Future research focusing on maternal, fetal and neonatal outcomes related to intrapartum IV fluid administration is still needed to develop protocols to prevent fluid overload and the associated morbidity for women and their infants.

**Implications for Practice**

It is now known that giving low risk women less IV fluid intrapartum does not result in a reduction of the number of babies that lose > 7% of their birth weight prior to hospital discharge. For the administration of intrapartum IV fluid volumes of < 2500 mls, there is no need to change current practice to reduce volumes infused in order to reduce newborn weight loss in breastfed infants. Although no controlled trials have compared the effect of larger intrapartum IV fluid volumes on newborn weight loss, the subgroup analysis in the FILL Trial suggests it may be helpful to be cautious about higher volumes of IV fluid. It is recommended that attention be paid to fluid volumes >2500 mls since this may be the threshold that results in greater weight loss in breastfed infants. For infants losing >10% of their birth weight, a review of the volume of fluid infused intrapartum should take place. For women receiving >2500 ml of IV fluid intrapartum, consideration could be given to the contribution this volume of fluid to the infant’s weight loss and care plans developed accordingly.

Elements of the clinical practice guideline developed for this trial are recommended for use in practice. These elements include 1) that caregivers routinely include hydration status as
part of their admission history and physical for labouring women (B-III), 2) that ongoing assessment of hydration status, following admission, for low risk women in labour should guide decision making regarding the appropriate volume of fluid to be given for management of a particular problem (B-III), 3) that caregivers should keep meticulous intrapartum fluid balance documentation for all women in labour receiving intravenous fluids ensuring that volumes infused are reconciled against the physiologic need for fluid and necessary adjustments made to ensure euvolemia (I-III), and 4) that whenever the care of the labouring woman is being handed over to another caregiver, the fluid volume already infused and the written fluid balance sheet should be an explicit part of the handover report (A-III). The importance of recording and communicating intake and output for the laboring woman and being mindful of the potential for overload are elements of good practice.

It is recommended that a thoughtful approach be taken to considering babies who lose >7% of their birth weight as babies with problematic breastfeeding. When almost half of breastfed babies lose this amount of weight, perhaps it is too low a percentage at which to present a clinical concern for caregivers. For infants who lose >10% of their birth weight prior to discharge, consideration could be given to reviewing the volume of fluid administered intrapartum. Volumes of intrapartum intravenous fluid > 2500 mls could be one of the possible explanations for this weight loss.
Conclusion

Approximately 59% of labouring women in the province of Ontario receive epidural analgesia and therefore have intravenous therapy initiated during their labours (Chapman, 2007), yet there are no published protocols or guidelines available to address fluid management in labour to optimize care for women and their infants. The absence of an evidence-based approach to intrapartum fluid management can result in fluid overload, with consequent maternal and newborn morbidity. The purpose of the FILL Trial was to evaluate a conservative approach to intrapartum IV fluid administration compared to usual IV fluid administration.

Restricting IV fluids in labour to a preload of 250 to 500 mls and an hourly infusion rate of 110 mls, compared to a more liberal policy of a preload of > 500 mls and an hourly infusion rate of 200 mls per hour, has no known benefits related to breastfed newborn weight loss > 7% prior to discharge. Further research is warranted to explore threshold effects and the effects of IV fluid volume on method of birth and newborn wellbeing in order to contribute to the creation of more evidence regarding safe volumes of fluid administration in labour for women and their infants.
References


The Fill Trial


http://www40.statcan.ca/myaccess.library.utoronto.ca/l01/cst01/demo04a.htm


doi: 10.1007/s00268-004-73833-7


Zamora, J. E., Rosaeg, O. P., Lindsay, M. P., & Crossan, M. L. (1996). Haemodynamic consequences and uterine contractions following 0.5 or 1.0 litre crystalloid infusion before

### Appendix A: Evidence Tables for Fluid Management in Surgical Populations: Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study author date</th>
<th>N</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results (p value)</th>
<th>Comments</th>
<th>Implications</th>
</tr>
</thead>
</table>
| Nisanevich (2005) | 156 | Intraoperative treatment Ctl=76 Tx=76 | Outcome 1 death
Outcome 2 Post op complications initial passage of flatus and feces, LOS, lab value differences
Outcome 3 LOS | No deaths in either group Ctl passed flatus and feces significantly later \( p<0.001 \) Ctl LOS significantly longer \( p=0.01 \) | Included a variety of surgical pts, elective intra-abdominal Used fluid algorithm | Support for conservative fluid administration= ↓ morbidity and LOS |
| Holte (2003) | N=12 | Tx=5ml/kg +electrolytes | Outcome 1 pulmonary function
Outcome 2 weight gain/urine output
Outcome 3 well being | Tx group lung function ↓ significantly x 8h 40ml/kg = ↑ weight gain and urine output \( p<0.05 \) ns | Volunteers 60+ years old | Liberal fluid impairs pulmonary function, inability to excrete excess fluid > 24h |
| Holte (2004) | n=48 | Tx=15ml/kg Ctl=40ml/kg | Outcome 1 pulmonary function
Outcome 2 well-being
Outcome 3 LOS | 40ml/kg improved pul function \( p<0.05 \) 40ml/kg ↓ well being, \( p<0.05 \), 40ml/kg ↓ LOS \( p<0.02 \) | of 80 patients approached, 28 refused Only low risk patients | Outcomes favoured liberal fluid, concluded high dose fluid decreases complication |
<table>
<thead>
<tr>
<th>Study</th>
<th>Tx</th>
<th>Ctl</th>
<th>Intervention</th>
<th>Outcome 1: Pulmonary function</th>
<th>Outcome 2: Time to defecation</th>
<th>Outcome 3: Coagulation</th>
<th>Outcome 4: LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holte (2007)</td>
<td>Tx-24</td>
<td>Ctl-24</td>
<td>Tx received restricted fluid protocol</td>
<td>ns</td>
<td>ns</td>
<td>Hypercoagulation in Ctl group</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fast track knee arthroscopy</td>
<td></td>
<td></td>
<td>Liberal fluid led to hypercoagulation, no other differences identified</td>
</tr>
<tr>
<td>Brandstrup (2005)</td>
<td>172 (140)</td>
<td>Tx 69 Ctl 72</td>
<td>Tx received restricted regimen, Ctl received standard regimen</td>
<td>Tx group less complications ( p &lt; 0.007 )</td>
<td>Tx group better tissue healing ( p &lt; 0.04 )</td>
<td>Tx group fewer deaths (ns) ( p &lt; 0.12 )</td>
<td>Interim analysis recalculated sample size to 140</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Restricted fluid regimen reduced postop complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobo (2002)</td>
<td>20</td>
<td>Tx 10 Ctl 10</td>
<td>Tx restricted regimen, Ctl standard regimen</td>
<td>Tx shorter time ( p &lt; 0.02 )</td>
<td>Tx shorter LOS ( p &lt; 0.001 )</td>
<td>Restricted fluid regimen reduced postop complications</td>
<td></td>
</tr>
</tbody>
</table>

Tx=treatment group, Ctl= control group, LOS= length of stay, NS=non significant, RL=Ringers Lactate IV solution
Appendix B: Search Strategy for Systematic Review

Cochrane Pregnancy & Childbirth Group: Search Strategies Information

Specialized register

Inclusion criteria

TOPIC SCOPE: Controlled trials comparing alternative forms of care used either during pregnancy (but not to terminate early pregnancy), or within 28 days of delivery.

STUDY DESIGN: A controlled trial has been defined as a trial involving humans in which allocation to the intervention has either been at random, or by some quasi-random method, such as by alternation, or on the basis of the case record number or date of birth.

These criteria have been applied fairly liberally to avoid excluding potentially useful studies involving concurrent comparisons of alternative policies. In other words, the register includes reports which, if necessary, can subsequently be rejected as methodologically inadequate by a member of the Group preparing a systematic review.

Hard copies of all trial reports identified through the searching activities described are obtained and reviewed by the Trials Search Co-ordinator to see if they meet the eligibility criteria. Reports are then added to the register. On the basis of the health topic(s) and/or form(s) of care covered, every record in the register is assigned by the editorial team to one or more review authors in the Cochrane Group, according to the agreed spheres of responsibility of each.

Electronic searches

(1) MEDLINE

The National Library of Medicine MEDLINE database has been searched back to 1966, and is updated weekly. The method of access and search strategy have been adjusted from time to time. The current search strategy, using OVID MEDLINE, is as follows:

1. clinical trial.pt
2. randomized.ti,ab
3. placebo.ti,ab.
4. dt.fs.
5. randomly.ti,ab.
6. trial.ti,ab.
7. groups.ti,ab.
8. or/1-7
9. exp Pregnancy/
10. exp Fetus/
11. exp Pregnancy Complications/
12. Infant, Newborn/
13. exp Postpartum Period/
14. exp Prenatal Diagnosis/
15. or/9-14
16. 8 and 15
17. Animals/
18. Humans/
19. 17 not (17 and 18)
20. 16 not 19

Lines 1-25 identify all possible RCTs. Lines 26-29 are to identify those relevant to the scope of the Group.

(2) The Cochrane Central register of Controlled Trials (CENTRAL)

The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library is searched using MeSH terms relevant to pregnancy and childbirth together with free text terms. This search is run quarterly.
The Fill Trial

with each new issue of *The Cochrane Library.*

#1 MeSH descriptor Pregnancy explode all trees
#2 MeSH descriptor Pregnancy Complications explode all trees
#3 MeSH descriptor Fetal Therapies explode all trees
#4 MeSH descriptor Labor Pain explode all trees
#5 MeSH descriptor Infant, Newborn explode all trees
#6 MeSH descriptor Fetus explode all trees
#7 MeSH descriptor Fetal Development explode all trees
#8 MeSH descriptor Fetal Membranes explode all trees
#9 MeSH descriptor Heart Rate, Fetal explode all trees
#10 MeSH descriptor Placenta explode all trees
#11 MeSH descriptor Placental Function Tests explode all trees
#12 MeSH descriptor Umbilical Cord explode all trees
#13 MeSH descriptor Prenatal Diagnosis explode all trees
#14 MeSH descriptor Uterine Monitoring explode all trees
#15 MeSH descriptor Pelvimetry explode all trees
#16 MeSH descriptor Fetal Monitoring explode all trees
#17 MeSH descriptor Obstetrical Nursing explode all trees
#18 MeSH descriptor Oxytocics explode all trees
#19 MeSH descriptor Tocolytic Agents explode all trees
#20 MeSH descriptor Tocolysis explode all trees
#21 MeSH descriptor Anesthesia, Obstetrical explode all trees
#22 MeSH descriptor Obstetric Surgical Procedures explode all trees
#23 MeSH descriptor Maternal Health Services explode all trees
#24 MeSH descriptor Maternal-Child Nursing explode all trees
#25 MeSH descriptor Analgesia, Obstetrical explode all trees
#26 MeSH descriptor Midwifery explode all trees
#27 MeSH descriptor Perinatal Care explode all trees
#28 MeSH descriptor Parity explode all trees
#29 MeSH descriptor Apgar Score explode all trees
#30 MeSH descriptor Postpartum Period explode all trees
#31 MeSH descriptor Breast Feeding explode all trees
#32 MeSH descriptor Milk, Human explode all trees
#33 pregnant
#34 fetus
#35 foetus
#36 fetal
#37 foetal
#38 newborn
#39 new next born
#40 birth or childbirth
#41 labor or laboring
#42 labour*
#43 antepart*
#44 prenatalt
#45 antenatal*
#46 perinatal*
#47 postnatal*
#48 postpart*
#49 caesar*
#50 cesar*
#51 obstetric*
#52 oxytocic*
#53 tocoly*
#54 placenta*
#55 prostaglandin*
#56 parturi*
#57 preeclampsia*
#58 pre next eclamp*
#59 eclamp*
#60 intrapart*
The CENTRAL search strategy was devised by Lynn Hampson with the assistance of Carol Lefebvre of the UK Cochrane Centre.

Hand searching
(1) Journals

Acta Anaesthesiologica Scandinavica (and supplements): from 1st issue, continuing prospectively
Acta Obstetrica et Gynecologica Scandinavica (and supplements): from 1950, continuing prospectively
Acta Paediatrica Scandinavica: from 1st issue through 1993; search stopped
American Journal of Clinical Nutrition: from 1st issue, continuing prospectively
American Journal of Diseases in Children: from 1950 through 1993; search stopped
American Journal of Obstetrics and Gynecology: from 1950, continuing prospectively
Anaesthesia and Intensive Care: from 1st issue, continuing prospectively
Anaesthesia: from 1950, continuing prospectively
Anesthesia and Analgesia: from 1st issue, continuing prospectively
Anesthesiology: from 1950, continuing prospectively
Archives of Disease in Childhood: from 1950 through 1993; search stopped
Australian and New Zealand Journal of Obstetrics and Gynaecology: from 1st issue, continuing prospectively
Birth: from 1st issue, continuing prospectively
BMJ: from 1950 through 1996; search stopped
British Journal of Anaesthesia: from 1950, continuing prospectively
British Journal of Obstetrics and Gynaecology: from 1st issue, continuing prospectively
Canadian Journal of Anaesthesia: from 1st issue, continuing prospectively
Canadian Medical Association Journal: from 1950; search stopped
Clinical Pharmacology and Therapeutics: from 1st issue; search stopped
Current Medical Research and Opinion: from 1st issue through 1993; search stopped
Developmental Medicine and Child Neurology: from 1st issue through 1993; search stopped
Early Human Development: from 1st issue through 1993; search stopped
European Journal of Obstetrics, Gynecology and Reproductive Biology: from 1st issue, continuing prospectively
Geburtshilfe und Frauenheilkunde: from 1950, continuing prospectively
Gynecology and Obstetric Investigation: from 1st issue, continuing prospectively
Infectious Diseases in Obstetrics and Gynecology: from 1st issue, continuing prospectively
International Journal of Gynaecology and Obstetrics: from 1st issue, continuing prospectively
International Journal of Obstetrical Anesthesia: from October 1994 through October 1995; from January 2003 continuing prospectively
JAMA: from 1st issue through 1996; search stopped
Journal of the American College of Surgeons: from 1950 through 2003; search stopped
Journal de Gynecologie, Obstetrique et Biologie de la Reproduction (Paris): from 1st issue through 1998; search stopped
Journal of International Medical Research: from 1st issue through 1993; search stopped
Journal of Nurse Midwifery: from 1st issue, continuing prospectively
Journal of Obstetrics and Gynaecology: from 1st issue, continuing prospectively
Journal of Obstetric, Gynecologic and Neonatal Nursing: from 1st issue through 1993; search stopped
Journal of Pediatrics: from 1950 through 1993; search stopped
Journal of Pediatric Gastroenterology and Nutrition: from 1st issue through 1993; search stopped

#61 puerper*
#62 episiotom*
#63 amnio*
#64 matern*
#65 gestation*
#66 lactati*
#67 breastfe*
#68 breast next fe*
#69 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)
The Cochrane Collaboration maintains a masterlist of all the journals handsearched throughout the Collaboration. Details can be found at: [http://www.cochrane.us/masterlist.asp](http://www.cochrane.us/masterlist.asp)

(2) Conference Proceedings

American College of Obstetricians and Gynecologists' Annual Meeting: 36th, 37th, 39th, 40th, 41st
American Society of Regional Anesthesia and Pain Medicine Annual Spring Meeting: 26th, 27th, 28th
Argentinean Congress of Perinatology: 3rd
Australian Perinatal Society: 14th
Australian Society of Anaesthetists National Scientific Congress: 58th
Birth Conference: 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th
British Congress of Obstetrics and Gynaecology: 23rd, 25th, 26th, 27th, 28th
British Maternal and Fetal Medicine Society: 6th
British Paediatric Association Annual Meeting: 14th, 15th, 27th, 60th, 61st, 62nd, 63rd, 65th
Congress of Nordic Federation of Societies of Obstetrics and Gynecology: 34th
European Congress of Allied Specialists in Maternal and Neonatal Care: 4th
European Congress of Obstetrical Anaesthesia and Analgesia: 1st
European Congress of Obstetrics and Gynaecology: 18th
European Congress of Perinatal Medicine: 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 14th, 15th, 16th
European Congress on Prostaglandins in Reproduction: 1st, 2nd
European Congress on Ultrasound in Medicine and Biology: 6th
Federation of the Asia-Oceania Perinatal Societies' Congress: 6th, 9th
International Anesthesia Research Society Clinical and Scientific Congress: 76th, 78th
International Confederation of Midwives Triennial Congress: 24th
International Conference of Maternity Care Researchers: 10th
International Congress on Psychosomatic Medicine in Obstetrics and Gynaecology: 3rd, 5th
International Scientific Meeting of the Royal College of Obstetricians and Gynaecologists: 4th
International Society for the Study of Hypertension in Pregnancy (ISSHP) European Branch: 1st
International Society for the Study of Hypertension in Pregnancy (ISSHP) World Branch: 1st, 2nd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 12th, 13th, 14th
Japanese Society of Obstetrics and Gynecology: 54th, 56th
Maternity Care Researchers International Conference: 10th
Nordic Federation of Societies of Obstetrics and Gynecology Congress: 34th
Obstetric Anaesthetists Association: 2005
Perinatal Society of Australia and New Zealand Annual Congress: 4th, 7th
Priorities in Perinatal Care in South Africa: 2nd, 4th, 7th, 9th, 10th, 11th, 12th, 14th, 15th, 16th, 17th
Society of Obstetricians and Gynaecologists of Canada Annual Meeting: 49th, 54th
Society of Perinatal Obstetricians' (USA) Annual Meeting: 3rd, 6th, 7th, 8th, 9th, 10th, 14th, 17th, 18th
Society for Gynecologic Investigation (USA) Annual Program: 31st, 34th, 37th, 39th, 40th
Other search strategies

(1) Surveys to identify unpublished and ongoing trials

During the second half of 1986 and early 1987, letters were sent to approximately 42,000 obstetricians and pediatricians in 18 countries in an attempt to identify unpublished controlled trials in perinatal medicine. The countries included in the survey were selected because they had generated more than 90% of the published reports of controlled trials in the Oxford Database of Perinatal Trials. This resulted in the notification of 395 unpublished randomized trials. Only 18 of the trials had been completed more than 2 years before the survey, a period during which at least 2300 reports of perinatal trials had been published. Of the 395 unpublished trials, 125 had ceased recruitment within the 2 years prior to the survey, 193 were actively recruiting at the time of the survey, and 59 were about to begin recruitment.

In 1991, prompted by the disappointing response to the earlier survey of individuals in an attempt to obtain information about unpublished and ongoing trials, a further, more focussed survey was conducted of clinical and academic institutions and funding agencies in the United Kingdom and North America to assess the feasibility of voluntary registration of trials. The experience gained in this and the earlier survey suggested that publication bias could not be addressed successfully by attempts to obtain information about unpublished trials retrospectively. This has led members of the Cochrane Pregnancy and Childbirth Group to support calls for prospective registration of trials, at inception.

(2) Current Awareness

ZETOC, The British Library's Electronic Table of Contents service sends the contents tables via e-mail of the journals listed below. The contents are reviewed by the Trials Search Co-ordinator. Hard copies of all possible reports of RCTs/CCTs relevant to the scope of the group are obtained, reviewed and added to the register by the Trials Search Co-ordinator if they meet the inclusion criteria.

ACOG Clinical Review
American Journal of Perinatology
Annali di Ostetricia Ginecologia Medicina Perinatale
Archives of Gynecology and Obstetrics
Chinese Journal of Obstetrics and Gynecology
Clinica e Investigacion en Ginecologia y Obstetricia
Clinical and Experimental Obstetrics and Gynecology
Clinical Obstetrics and Gynecology
Complementary Therapies in Nursing and Midwifery
Controlled Clinical Trials
Current Opinion in Obstetrics and Gynecology
Current Problems in Obstetrics Gynecology and Fertility
Early Pregnancy
Fetal and Maternal Medicine Review
Fetal Diagnosis and Therapy
Ginecologia y Obstetricia de Mexico
Giornale Italiano di Ostetricia e Ginecologia
Gynakologisch Geburts hilfliche Rundschau
Hypertension in Pregnancy
International Journal of Childbirth Education
Italian Journal of Gynaecology and Obstetrics
Journal de Gynecologie, Obstetrique et Biologie de la Reproduction (Paris)
Journal of Maternal Fetal Medicine
Journal of Paediatrics Obstetrics and Gynaecology
Journal of Perinatology
Journal of Psychosomatic Obstetrics and Gynaecology
Journal- SOGC
Journal of the Medical Association of Thailand
Obstetrical and Gynecological Survey
Prenatal and Neonatal Medicine
Prenatal Diagnosis
Summary of Search Strategy Terms

Search Strategy : Dehydration
Fetal Monitoring Hedge: Fetal Monitoring, exp Heart Rate, Fetal, fhr:mp., ((fetal or foetal) adj2 monitor:).mp. (fetal or foetal) adj2 rate).mp.,

Search Strategy: Fluid Hedge

Search Strategy Fever: exp fever, fever:mp, febrile:mp
Search Strategy Anesthesia: Epidural analgesia, exp Injections, Epidural analgesia analgesia, epidural analgesia analgesia.mp
## Appendix C: Evidence Tables for Fluid Management in Intrapartum Care Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study author date</th>
<th>n</th>
<th>Total Volume Infused</th>
<th>Intervention</th>
<th>Outcomes Maternal/Fetal/Neonatal</th>
<th>Results ((p \text{ value}))</th>
<th>Adverse Events Reported</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Shrivastiva (2009) | 289   | Not reported         | Group 1: NS  
Group 2: NS+5% dextrose 
Group 3: NS+10% dextrose | Outcome 1: Labour length  
Outcome 2: mode of delivery  
Outcome 3: oxytocin use | \(P < 0.02\)  
\(\text{ns}\)  
\(\text{ns}\) | None reported | Caesarean patients not included in analysis-11 randomized patients not included in analysis  
opaque envelopes for randomization |
| Shannon 1998     | 30    | Not reported         | Group 1 no preload  
Group 2 preloaded 500 ml RL | Outcome 1: hypotension  
Outcome 2: FHR: no difference | Not reported | No blinding to measurements |
| Eslamian 2006    | 300   | Mean Volumes Reported | Group 1 IV run at 125ml/h  
Group 2 IV run at 250ml/h | Outcome 1: labour length significantly greater in 125ml group  
Outcome 2: oxytocin use: significantly higher in 125ml group  
Outcome 3: c section | \(P < 0.0001\)  
\(P < 0.001\)  
\(\text{ns}\) | Not reported | No blinding  
Definition of 'prolonged labour’ not clinically useful (>10h)  
Study site does not offer epidural analgesia |
| Garite 2000      | 195   | Reported             | Group 1 IV run at 125ml/h  
Group 2 IV run at 250ml/h | Outcome 1: labour length significantly greater in 125ml group  
Outcome 2&3: trend to longer labour, use of oxytocin and c/s in 125ml group | \(P < 0.04\)  
\(\text{ns}\)  
\(\text{ns}\) | Not reported | No blinding  
Definition of 'prolonged labour’ not clinically useful (>12h)  
assumes dehydration volume of IV infused prior to intervention unknown- could alter effects |
| Kubli 2003       | 182   | Not reported         | Group 1 no preload  
Group 2 preload of 7mL/kg | Outcome 1: Hypotension no difference  
Outcome 2: FHR deterioration no difference | \(P < 0.6\)  
\(1.54-2.7\)  
\(P > 0.7\)  
\(1.6-13\) | Not reported | Did not have sufficient power to detect a difference |

Legend: IV=intravenous, RL=Ringers Lactate, FHR=fetal heart rate, c/s=caesarean section,
<table>
<thead>
<tr>
<th>Study author date</th>
<th>n</th>
<th>Total Volume Infused</th>
<th>Intervention</th>
<th>Outcomes Maternal/Fetal/Neonatal</th>
<th>Results (p value) e.g. reduction in absolute risk, relative risk (95%CI)</th>
<th>Adverse Events Reported</th>
<th>Comments (specific populations, strengths / weaknesses, external validity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheek 1996</td>
<td>34</td>
<td>G1=11 G2=8 G3=11</td>
<td>Not known</td>
<td>Group 1: no preload Group 2: 0.5 L NS Group 3: 1.0 L NS</td>
<td>Outcome 1: HYPOTENSION no difference</td>
<td>Inadequate data reported to calculate RRR</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 2: UTERINE ACTIVITY no difference in Group 1 and 2, decrease in G 3</td>
<td>Outcome 2: p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 3: p&lt;0.05</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Kinsella 2000</td>
<td>100</td>
<td>G1=49 G2=46</td>
<td>Not known</td>
<td>Group 1: preload of 1 L RL Group 2: no preload, IV TKVO</td>
<td>Outcome 1: HYPOTENSION No difference</td>
<td>Outcome 1 p=0.4</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Outcome 2: FHR CHANGES No difference</td>
<td>Outcome 2 p=0.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 3: FHR CHANGES POST EPIDURAL ANALGESIA No difference</td>
<td>Outcome 3 p=0.08</td>
<td></td>
</tr>
<tr>
<td>Zamora 1993</td>
<td>92</td>
<td>G1=46 G2=46</td>
<td>Not known</td>
<td>Group 1: 0.5 L RL Group 2: 1.0 L RL</td>
<td>Outcome 1: HYPOTENSION No difference</td>
<td>None reported</td>
<td>Infusing 1 L delayed epidural analgesia, did not protect against hypotension The 2 abnormal FHR were in women with hypotension Study terminated after interim analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 2: FHR CHANGES No difference</td>
<td>Outcome 3: p&lt;0.05</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 3: FREQUENCY OF CONTRACTIONS ↓ in contraction rate in 1L group</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome 3: MEAN ARTERIAL PRESSURE no difference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = normal saline, RL=ringers lactate, TKVO= to keep vein open, FHR=fetal heart rate, L=liter, LOS=length of stay
### Levels of Evidence

**A Research Design Rating**
- **I** Evidence from randomized controlled trials
- **II-1** Evidence from controlled trials without randomization
- **II-2** Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group
- **II-3** Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here
- **III** Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

**B. Quality (internal validity) rating**
- **Good** A study that meets all design-specific criteria *well*
- **Fair** A study that does not meet (or it is not clear that it meets) at least one design-specific criterion *but has no known “fatal flaw”*
- **Poor** A study that has at least one design-specific “fatal flaw” or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations

### Recommendations Grades for Specific Clinical Preventive Actions

- **A** The CTF concludes that there is **good** evidence to recommend the clinical preventive action
- **B** The CTF concludes that there is **fair** evidence to recommend the clinical preventive action
- **C** The CTF concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against use of the clinical preventive action, however, other factors may influence decision making
- **D** The CTF concludes that there is **fair** evidence to recommend against the clinical preventive action
- **E** The CTF concludes that there is **good** evidence to recommend against the clinical preventive actions
- **I** The CTF concludes that there is **insufficient** evidence (in quality or quantity) to make a recommendation, however other factors may influence decision-making

The CTF recognizes that in many cases patient specific factors need to be considered and discussed such as the value the patient places on the clinical preventive action: its possible positive and negative outcomes; and the context and or personal circumstances of the patient. In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.

Appendix E: The FILL Trial Maneuver

Woman presents in Early Labour Assessment Area, No history of vomiting or diarrhea in last 24 hours

Low Risk Pregnancy confirmed
Wanting epidural analgesia

Eligibility criteria confirmed
Woman recruited
Baseline data collected

Randomized

Usual Care
- IV initiated epidural administered
- delivery
- Outcomes measured at discharge

Conservative Care
- IV initiated epidural administered
- delivery
- Outcomes measured at discharge
Appendix F: The Breastfeeding Self-Efficacy Scale

Breastfeeding Self-Efficacy Scale – Short Form

For each of the following statements, please choose the answer that best describes how confident you are with breastfeeding your new baby. Please mark your answer by circling the number that is closest to how you feel. There is no right or wrong answer.

1 = not at all confident  
2 = not very confident  
3 = sometimes confident  
4 = confident  
5 = very confident

<table>
<thead>
<tr>
<th>Very Confident</th>
<th>Not at all Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I can always determine that my baby is getting enough milk</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>2 I can always successfully cope with breastfeeding like I have with other challenging tasks</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>3 I can always breastfeed my baby without using formula as a supplement</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>4 I can always ensure that my baby is properly latched on for the whole feeding</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>5 I can always manage the breastfeeding situation to my satisfaction</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>6 I can always manage to breastfeed even if my baby is crying</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>7 I can always keep wanting to breastfeed</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>8 I can always comfortably breastfeed with my family members present</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>9 I can always be satisfied with my breastfeeding experience</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>10 I can always deal with the fact that breastfeeding can be time consuming</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>11 I can always finish feeding my baby on one breast before switching to the other breast</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>12 I can always continue to breastfeed my baby for every feeding</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>13 I can always manage to keep up with my baby’s breastfeeding demands</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>14 I can always tell when my baby is finished breastfeeding</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

©Dr. Cindy-Lee Dennis

15. Has your baby had any other food other than breastmilk? Yes No
Appendix G: Data Collection Fields Exported from the In-House Hospital Databases

Maternal Data

Mother’s Date of Birth  
Date of admission  
Time of admission  
Gestational Age  
Date epidural initiated  
Time epidural initiated  

Gravida  
Parity  Live Births  

Was oxytocin ever received?  

Was a caesarean section performed?  

Newborn Data  

Date of Delivery  
Time of Delivery  
Is mom breastfeeding?  Y  N  
Sex  M  F  
Birth weight in grams  
Mode of delivery  
spontaneous  
forceps  
vacuum extraction  
caesarean section breech delivery  

Newborn resuscitation  Y  N  

Was baby admitted to NICU?  Y  N  

Was a referral made to breastfeeding clinic?  Y  N  

Was supplementation given in Combined Care  Y  N  

Was infant’s discharge delayed due to breastfeeding?  Y  N
### Inclusion criteria (must be answered ‘yes’ to be eligible)

1. The woman is in early labour or expected to return to Triage in early labour

2. She is categorized as Risk Grade Score A on the OAR (+ or - history of previous caesarean section)

3. The woman is planning to breastfeed.

4. The woman planning on having epidural labour analgesia

5. The fetus is between 37 and 42 weeks’ gestation

### Exclusion criteria (must be answered ‘no’ to be eligible)

6. The woman has had diarrhea, vomiting or significantly reduced fluid intake vomiting in the last 24 hours

7. The woman has a history of breast surgery

8. The woman unable to read and write English

9. The woman is planning discharge before 48 hours (please confirm that the woman understands this-she will not go home ‘early’)

10. Multiparous and > 4 cm dilated, or primiparous and > 5 cm dilated or expected to deliver within the next 4 hours

---

**Woman willing to participate**

- **Yes** (1) ○ **No** (2) ○ If no, please indicate reason

---

**Previous Breastfeeding Experience beyond postpartum discharge?**

- **Yes** (1) ○ **No** (2) ○

---

**Assigned study group** (go to [www.randomize.net](http://www.randomize.net))

- ○ conservative fluid management group ○ usual fluid management group

---

**Date and Time of Randomization**

<table>
<thead>
<tr>
<th>YYYY</th>
<th>MM</th>
<th>DD</th>
<th>24 hour clock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nurse’s Signature: ____________________ Date: ____________________ 12/31/2008
## The FILL Trial Fluid Balance Sheet

### Conservative Care

<table>
<thead>
<tr>
<th>Pump #</th>
<th>Hourly Rate:</th>
<th>cc/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date IV Initiated</th>
<th>Time IV initiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>YYYY MM DD</td>
<td>Hour: min use 24 hour clock</td>
</tr>
<tr>
<td>(Example: 2023, 04, 15, 08:00)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epidural Preload volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>cc</td>
</tr>
</tbody>
</table>

### Total IV fluid infused q 4 hourly totals

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume</th>
<th>Time</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 4 hours</td>
<td></td>
<td>5th 4 hours</td>
<td></td>
</tr>
<tr>
<td>2nd 4 hours</td>
<td>cc</td>
<td>6th 4 hours</td>
<td>cc</td>
</tr>
<tr>
<td>3rd 4 hours</td>
<td>cc</td>
<td>7th 4 hours</td>
<td>cc</td>
</tr>
<tr>
<td>4th 4 hours</td>
<td>cc</td>
<td>8th 4 hours</td>
<td>cc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bolus given for abnormal FHR tracing</th>
<th>(check mark for each bolus given)</th>
</tr>
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<table>
<thead>
<tr>
<th>Bolus given to replace volumes</th>
<th>(check mark for each bolus given)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Acetaminophen for fever (not bolus)</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>proBNP sample sent</th>
<th>yes</th>
<th>no</th>
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</table>

<table>
<thead>
<tr>
<th>Over 2500 cc infused?</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Total volume of IV fluid infused at time of birth</th>
<th>cc</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>RN signature:</th>
<th>RN name:</th>
</tr>
</thead>
</table>
The FILL Trial Fluid Balance Sheet

Mother’s ID

Usual Care

Was an infusion pump used for mainline infusion  yes □  no □ (should be NO)

Date IV Initiated

YYYY  MM  DD

Time IV initiated

Hour:min use 24 hour clock

Epidural Preload Volume (should be > 500ml)  cc

Bolus given for abnormal FHR tracing
(place a check mark for each bolus given)

Bolus given to replace volumes
(place a check mark for each bolus given)

Bolus for fever
(place a check mark for each bolus given)

Acetaminophen for fever  yes □  no □ (should be NO)

proBNP sample sent  yes □  no □

Total volume of IV fluid infused at time of birth  mls

RN signature ___________________________  RN name ___________________________
### FILL Trial Newborn Data

**Mother’s ID**

<p>| | | |</p>
<table>
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<tr>
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**Mother’s Date of Birth**

<p>| | | | |</p>
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<th></th>
<th></th>
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<table>
<thead>
<tr>
<th>1. Baby’s Date of birth</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>YYYY</td>
<td>MM</td>
<td>DD</td>
<td></td>
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</table>

To be obtained from the Electronic Patient Record system:


<table>
<thead>
<tr>
<th>4. Newborn Weights (in grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Recorded Weight</strong></td>
</tr>
<tr>
<td><strong>Second recorded weight</strong></td>
</tr>
<tr>
<td><strong>Third recorded weight</strong></td>
</tr>
<tr>
<td><strong>Fourth recorded weight</strong></td>
</tr>
<tr>
<td><strong>Fifth recorded weight</strong></td>
</tr>
<tr>
<td><strong>Sixth recorded weight</strong></td>
</tr>
<tr>
<td><strong>Lowest Recorded Weight</strong></td>
</tr>
</tbody>
</table>
# Appendix I  Data Safety Monitoring Committee Charter

## 1. Introduction

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of trial plus ISRCTN and/or EUDRACT number</td>
<td><strong>The FILL Trial, “Fluid in Low Risk Labour”</strong></td>
</tr>
<tr>
<td>Objectives of trial, including interventions being investigated</td>
<td>The trial objectives are to evaluate a conservative approach to fluid management in low risk labour for women receiving epidural analgesia. Primary outcome: Breastfed newborn weight loss &gt; 7% at discharge from hospital (48h) Secondary outcomes: 1) Breastfeeding Self Efficacy 2) breastfeeding exclusivity 3) breastfeeding clinic appointments</td>
</tr>
<tr>
<td>Outline of scope of charter</td>
<td>The purpose of this document is to describe the roles and responsibilities of the Data Safety Monitoring Committee (DSMC) for the FILL Trial, including the timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings and statistical issues.</td>
</tr>
</tbody>
</table>

## 2. Roles and responsibilities

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
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</thead>
<tbody>
<tr>
<td>A broad statement of the aims of the committee</td>
<td>To safeguard the interests of trial participants, potential participants and investigators and to assess the safety and efficacy of the trial’s interventions.</td>
</tr>
<tr>
<td>Terms of reference</td>
<td>DSMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial. The DSMC should receive and review any adverse event data from this trial and provide advice on the conduct of the trial to the PhD Supervisory Committee.</td>
</tr>
<tr>
<td>Specific roles of DSMC</td>
<td>To undertake interim review of the trial’s progress by: • monitoring evidence for treatment harm e.g. serious adverse events, deaths, any newborn admission to the NICU &gt; 48 hours, any maternal admission to ICU.</td>
</tr>
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</table>

## 3. Before, or early in to, the trial

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whether the DSMC will have input into the protocol</td>
<td>Before recruitment began the trial will be approved by the IRB at the participating site. Potential DSMC members were familiar with the trial proposal and accepted the invitation to participate.</td>
</tr>
<tr>
<td>Whether the DSMC will meet before the start of the trial</td>
<td>As needed.</td>
</tr>
<tr>
<td>Any specific regulatory issues</td>
<td>None.</td>
</tr>
<tr>
<td>Whether members of the DSMC will have a contract</td>
<td>All members of the committee have agreed by email to be part of the committee</td>
</tr>
</tbody>
</table>

## 4. Composition

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
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</table>
| Membership and size of the DSMC | The membership consists of 3 individuals. Members have been chosen because they are experienced in trials and/or the clinical area relevant to the trial. The members will be independent of the trial (e.g. should not be involved with the trial in any other way or have some involvement that could impact on the trial). Members should not serve on DSMCs of similar, concurrently active trials as this could compromise the independence of the trial and possibly the confidentiality of the results of the individual trials. Any competing interests, both real and potential, should be declared. The members of the DSMC for the FILL trial are:  
1. Dr Jon Barrett, Maternal Fetal Medicine specialist, trialist, Sunnybrook Health Sciences Centre  
2. Dr Elizabeth Asztalos, Neonatologist, Director of the Maternal Infant Child Research Unit, Sunnybrook Health Sciences Centre  
3. Sharyn Gibbins, Neonatal Nurse Practitioner, Women and Babies Program, Sunnybrook Health Sciences Centre |
| The chair, how they are chosen and the chair’s role. (Likewise, if relevant, the vice-chairman) | The chair, Dr Asztalos, was chosen as an experienced neonatologist and researcher. The Chair is expected to convene, facilitate and summarise discussions. |
| The responsibilities of the PI and other members of the Steering Committee | The PI, Dr Ellen Hodnett, will be available to answer questions from the DSMC. Jo Watson, the trial coordinator/doctoral candidate, will prepare reports of any adverse events with Dr Hodnett. |
### 5. Relationships

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarification of whether the DSMC are advisory (make recommendations) or executive (make decisions)</td>
<td>The DSMC are advisory to the Thesis Committee.</td>
</tr>
<tr>
<td>Any payments to DSMC members</td>
<td>The FILL Trial does not expect to pay DSMC members or their employers.</td>
</tr>
<tr>
<td>The need for DSMC members to disclose information about any competing interests</td>
<td>Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility.</td>
</tr>
</tbody>
</table>

### 6. Organisation of DSMC meetings

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected frequency of DSMC meetings</td>
<td>The DSMC will be convened to consider each adverse event that occurs and would normally expect to return the report of their deliberations to the trial coordinator within 2 weeks of notification of an adverse event.</td>
</tr>
<tr>
<td>Whether meetings will be face-to-face or by teleconference</td>
<td>Normally, communication will be by email. Teleconferences and face-to-face meetings could be organized if needed (for example if consensus was not possible by e-mail correspondence).</td>
</tr>
</tbody>
</table>

### 7. Trial documentation and procedures to ensure confidentiality and proper communication

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended content of material to be circulated to the DSMC</td>
<td>For adverse events: The trial coordinator will provide the DSMC chair with all the details of the event. Any identifiers and the treatment allocation will be removed from the information provided. Only the final reports prepared by the DSMC will be shared with members of the PhD Supervisory Committee. The DSMC will be blinded to the identity of the treatment arms.</td>
</tr>
<tr>
<td>Will the DSMC be blinded to the treatment allocation?</td>
<td>Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DSMC members. The PI and the trial coordinator/dottoral candidate will collate any such information and communicate this to the DSMC.</td>
</tr>
<tr>
<td>Who will be responsible for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)</td>
<td>The chair will communicate in writing with the other members of the DSMC and collate their responses. She will draft the reports of the committee's decisions. Reports regarding adverse events will be returned to the trial coordinator and PI.</td>
</tr>
<tr>
<td>To whom the DSMC will communicate the decisions/recommendations that are reached</td>
<td></td>
</tr>
</tbody>
</table>

### 8. Decision making

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>DETAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>What decisions/recommendations will be open to the DSMC</td>
<td>The possible recommendations are:</td>
</tr>
<tr>
<td>The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules</td>
<td>• No action needed, trial continues as planned</td>
</tr>
<tr>
<td>How decisions or recommendations will be reached within the DSMC</td>
<td>• Early stopping due to safety concerns. No interim analysis planned</td>
</tr>
<tr>
<td>When the DSMC is quorate for decision-making</td>
<td>The role of the chair should be to summarise discussions and encourage consensus. In each area of discussion the chair should give her opinion last. Every effort should be made for the DSMC to reach a consensus. If the DSMC cannot achieve consensus, a vote should be taken, although details of the vote should not be routinely included in the report to the PhD Supervisory Committee.</td>
</tr>
<tr>
<td></td>
<td>No decision will be made without input from all members of the DSMC.</td>
</tr>
</tbody>
</table>
### 9. Reporting

<table>
<thead>
<tr>
<th>To whom the DSMC will report their recommendations/decisions, and in what form</th>
<th>See sections 7 and 8 above.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What will be done in the instances of disagreement between the DSMC and the body to which they report</td>
<td>The PhD Supervisory Committee has ultimate responsibility for the trial and assumes primacy. However, the PhD Supervisory Committee will report to DSMC on the actions taken in response to the DSMC’s recommendations. If the DSMC has serious problems or concerns with the PhD Supervisory Committee decision, a meeting of these groups should be convened by the Dr Hodnett to fully discuss the issues. Data or information to be shared at such a meeting would depend upon the action proposed and the DSMC’s concerns.</td>
</tr>
</tbody>
</table>

### 10. After the trial

<table>
<thead>
<tr>
<th>Publication of results</th>
<th>The PI has responsibility that trial results will be published in a correct and timely manner. The PhD Supervisory Committee is the committee that will oversee this process. DSMC members will be named (unless they specifically ask not to be) in the primary published report.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The information about the DSMC that will be included in published trial reports</td>
<td></td>
</tr>
</tbody>
</table>
Please consider participating in The FILL Trial
(Fluid In Low risk Labour) A study about IV fluid in labour

What is the best way to manage IV fluid during labour?
There are no established policies or guidelines for managing fluid in labour. We do not know the best way to administer intravenous fluid while you are labouring.

What is the Fluid in Low risk Labour trial?
The FILL trial is designed to determine if a conservative approach to IV fluid in labour prevents too much fluid and improves outcomes for you and your baby.

What is involved for me to participate in the FILL trial?
Participation in the study involves the following:
1. If you are receiving usual care, your IV will be administered according to current practice
2. If you are in the treatment group, your IV will be administered according to the study protocol.
3. A research assistant will collect information from your hospital chart about the well being of you and your baby.
4. For both groups, a sample of cord blood will be sent to the lab and you will be asked to complete a short questionnaire before you are discharged home
5. In all other respects, the nursing and medical care you and your baby receive will be no different as a result of your participation in this study

What are the risks and benefits of participating in the Fluid In Low risk Labour Trial?
There are no known harms to you or your baby from participating in this trial.
You may or may not experience any direct benefit from participating in this study, but your participation might improve care for women and babies in the future.

How can I find out more about the Fluid in Low risk Labour Trial?
You can speak to your own caregiver or your can contact the study investigator, Jo Watson RN, PhD(c), a PhD candidate at the Lawrence Bloomberg, Faculty of Nursing, University of Toronto at 416 323 6400, ext 4289 or jo.watson@utoronto.ca.
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Full Study Title: The FILL Trial: The effect of conservative versus usual intrapartum fluid management in women with epidural analgesia on breastfed newborn weight loss

Principal Investigator: Jo Watson, Perinatal & Gynaecology Program
Sponsor: Sunnybrook Health Sciences Centre Practice Based Research Award

INFORMED CONSENT

You are being asked to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the study, conservative fluid management in labour, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. You may take as much time as you wish to decide whether or not to participate. Please ask the study staff or one of the investigator(s) to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION

You are being asked to consider participating in this study because your labour is considered to be low risk, you would like to have an epidural and you are planning to breastfeed.

The FILL trial is designed to determine if a conservative approach to intravenous (IV) fluid in labour improves outcomes for you and your baby. A conservative approach may lead to less weight loss for your breastfed baby. There are no established policies or guidelines for managing fluid in labour and we do not know the best way to administer intravenous fluid while you are in labour.

WHAT IS THE USUAL TREATMENT?

Usual intrapartum fluid management includes the initiation of intravenous therapy prior to epidural analgesia administration or when intravenous drugs need to be administered. Fluid given before an epidural ranges from 500ml to 1000ml of Ringers Lactate and IV fluid is then administered throughout labour to maintain hydration. Extra amounts of fluid are given to treat a mother’s fever. Hourly infusion volumes vary from 125ml to 250 ml per hour or greater.
You may not receive the usual treatment for fluid administration in labour if you decide to participate in this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare the effects (good and bad) of conservative fluid management compared to usual intrapartum fluid management on you and your baby's initial weight loss to see which is better.

WHAT WILL HAPPEN DURING THIS STUDY?

Women in the conservative care group will receive 250-500 ml of IV fluid before their epidural and the infusion will continue at the hourly rate of 75 to 100 ml per hour. Maternal fever will be treated with acetaminophen.

Participants in this study will be randomly (by chance) placed in one of two study groups. Neither you, the study staff nor the investigator, can influence which group you are in. You will have an equal chance of being placed in either group. You and the study staff will know which group you are in.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

It is anticipated that about 200 women will participate in this single site study at Sunnybrook Health Sciences Centre. The length of this study for participants is from the time of admission into the Labour and Delivery Unit until you and your baby are discharged home in approximately 2-3 days. The entire study is expected to take about one year to complete.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you decide to participate in this study you will be asked to do the following:

- have an intravenous line (IV). The purpose of the IV is to be sure you are well hydrated and to replace whatever fluid you are losing during labour because you are not eating and drinking normally.

- if you are receiving usual care, your IV will be administered according to current practice.

- if you are receiving conservative care, your IV will be administered according to the study protocol.

- at the time of delivery, a sample of blood will be taken from your baby's umbilical cord in the same way that other samples of blood are taken at delivery. The specimens will be taken to measure the presence of a protein in your baby’s cord blood. The specimen will be used for this study only. Samples will be sent to the hospital laboratory and frozen until the end of the study when all the samples will be analyzed together. The sample will be linked to whether you were in the conservative fluid group or the usual care group. Samples will be destroyed after the study following hospital policy for disposal of blood specimens.

- have study personnel collect information from your hospital chart about the well being of you and your baby.

- complete a short questionnaire before your discharge about your breastfeeding experience. The questionnaire takes less than 10 minutes to complete (you may choose not to answer any questions in the questionnaire).
-In all other respects, the nursing and medical care you and your baby receive will be no different as a result of your participation in this study.

You may choose at any time to not to participate in any part of this study.

**WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?**

There are no known harms to you or your baby from participating in this study. If you decide to take part in this study, you should contact Jo Watson, Perinatal & Gynaecology Program, 416 323 6400 x4289 about any side effects or study-related injuries that you experience.

**WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**

You may or may not benefit directly from participating in this study. Your participation may improve care for women and babies in the future.

**CAN PARTICIPATION IN THIS STUDY END EARLY?**

The investigator may decide to remove you from this study without your consent for any of the following reasons:

- The investigator decides that continuing in this study would be harmful to you.
- You are unable or unwilling to follow the study procedures.

If you are removed from this study, the investigator will discuss the reasons with you and plans will be made for your continued care outside of the study. You can also choose to end your participation at any time. If you withdraw voluntarily from the study or at the request of your doctor, you are encouraged to contact Jo Watson, Perinatal & Gynaecology Program, 416 323 6400 x4289 immediately. You may be asked questions about your experience in the study, and to cooperate in having whatever laboratory tests and physical examinations considered necessary to safely stop your study involvement.

**WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?**

Participation in this study will not involve any additional costs to you or your private health care insurer.

**ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?**

You will not be paid to participate in this study.

**WHAT OTHER CHOICES ARE THERE?**

If you decide not to participate in this study, you will receive usual intrapartum fluid care.

**DOES THE INVESTIGATOR HAVE ANY CONFLICTS OF INTEREST?**

The investigator does not have any conflicts of interest.

**WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?**

All participants in a research study have the following rights:
1. You have the right to have this form and all information concerning this study explained to you.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact Jo Watson, Perinatal & Gynaecology Program, 416 323 6400 x4289 immediately.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator) Jo Watson, Perinatal & Gynaecology Program, 416 323 6400 x4289. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Philip C. Hébert, Chair of the Sunnybrook Research Ethics Board at (416) 480-4276.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.

8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff, and the Sunnybrook Research Ethics Board, will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 7 years.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT

Full Study Title: The FILL Trial: The effect of conservative versus usual intrapartum fluid management in women with epidural analgesia on breastfed newborn weight loss

Name of Participant: ________________________________________

Participant/Substitute decision-maker
By signing this form, I confirm that:
• This research study has been fully explained to me and all of my questions answered to my satisfaction
• I understand the requirements of participating in this research study
• I have been informed of the risks and benefits, if any, of participating in this research study
• I have been informed of any alternatives to participating in this research study
• I have read each page of this form
• I authorize access to my personal health information (medical record) and research study data as explained in this form
• I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study
• This informed consent document will be placed in my medical records

____________________________        ____________________________        _____________________
Name of participant/Substitute decision-maker (print)    Signature             Date

Person obtaining consent
By signing this form, I confirm that:
• I have explained this study and its purpose to the participant named above
• I have answered all questions asked by the participant
• I will give a copy of this signed and dated document to the participant

____________________________        ____________________________        _____________________
Name of Person obtaining consent (print)             Signature                       Date

Statement of Investigator
I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

____________________________        ____________________________        _____________________
Name of Investigator (print)                    Signature                           Date

ASSISTANCE DECLARATION □ (check here if not applicable)
The participant/substitute decision-maker was assisted during the consent process as follows: the consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, the participant/substitute decision-maker.

☐ The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that that participant/substitute decision-maker has understood the information translated.

__________________________        ____________________________        _____________________
Name of Person Assisting (Print)             Signature                       Date
### Appendix L  Recruitment Summary

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## Appendix L  Reasons for Vacuum and Forceps Deliveries

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<th>Usual Care (n=16)</th>
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