Association between intravenous fluids during labour and primary postpartum haemorrhage: A retrospective cohort study

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Abstract

Objective: To evaluate whether the administration of high-volume intravenous (IV) fluids during labour (> 2500 mL) increases the risk of primary postpartum haemorrhage (PPH) and other adverse outcomes for women with a term, singleton pregnancy, in comparison to low-volume IV fluids during labour (<2500 mL). Design: Retrospective cohort study Setting: Tertiary referral hospital in Sydney, Australia Sample: 1023 women with a live singleton fetus in a cephalic presentation; planning a vaginal birth; and admitted for labour and birth care between 37 - 42 weeks gestation. Methods: The study factor was IV fluids during labour. Birth and postnatal data were obtained from electronic medical records and paper fluid order documentation. Multivariable logistic regression and multiple imputation were used to explore the relationship between volume of IV fluids in labour and PPH. Main outcome measures: The primary outcome was primary PPH (> 500mL). Secondary outcomes included caesarean section and major perineal injury. Results: 1023 participants were included of which 339 had a primary PPH (33.1%). There was no association between high-volume IV fluids and PPH after adjusting for demographic and clinical factors (Adjusted odds ratio [OR adj] 1.02 95% confidence interval [95%CI] 0.72, 1.44). However, there was a positive association between high-volume IV fluids and caesarean section (OR adj 1.99; 95%CI 1.4, 2.8). Conclusion: These findings are important to further knowledge relating to administration of IV fluids in labour and the potential impact of this common practice. It identifies future research priorities around documentation of IV fluids and their relationship with pregnancy and perinatal outcomes.
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\textbf{ABSTRACT}

\textbf{Objective:} To evaluate whether the administration of high-volume intravenous (IV) fluids during labour (>2500 mL) increases the risk of primary postpartum haemorrhage (PPH) and other adverse outcomes for women with a term, singleton pregnancy, in comparison to low-volume IV fluids during labour (<2500 mL).

\textbf{Design:} Retrospective cohort study

\textbf{Setting:} Tertiary referral hospital in Sydney, Australia

\textbf{Sample:} 1023 women with a live singleton fetus in a cephalic presentation; planning a vaginal birth; and admitted for labour and birth care between 37 - 42 weeks gestation.

\textbf{Methods:} The study factor was IV fluids during labour. Birth and postnatal data were obtained from electronic medical records and paper fluid order documentation. Multivariable logistic regression and multiple imputation were used to explore the relationship between volume of IV fluids in labour and PPH.

\textbf{Main outcome measures:} The primary outcome was primary PPH (>500mL). Secondary outcomes included caesarean section and major perineal injury.

\textbf{Results:} 1023 participants were included of which 339 had a primary PPH (33.1%). There was no association between high-volume IV fluids and PPH after adjusting for demographic and clinical factors (Adjusted odds
ratio \( \text{OR}_{\text{adj}} 1.02 \) 95% confidence interval \( \text{[95\% CI] 0.72, 1.44} \). However, there was a positive association between high-volume IV fluids and caesarean section \( \text{OR}_{\text{adj}} 1.99; \text{95\% CI 1.4, 2.8} \).

**Conclusion:** These findings are important to further knowledge relating to administration of IV fluids in labour and the potential impact of this common practice. It identifies future research priorities around documentation of IV fluids and their relationship with pregnancy and perinatal outcomes.

**MAIN MANUSCRIPT**

1.0 Introduction

Primary postpartum haemorrhage (PPH) is one of the most common complications of childbirth and a major cause of maternal mortality and morbidity worldwide.\(^{(1-5)}\) The World Health Organization (WHO) defines primary PPH as a maternal blood loss \( \geq 500 \text{ mL} \) within the first 24 hours of giving birth.\(^{(4, 5)}\) Women who experience a primary PPH commonly require greater levels of clinical intervention and care immediately after the birth of their child and into the postpartum period.\(^{(6)}\)

The most common cause of primary PPH is uterine atony contributing to 70-80% of all primary PPHs.\(^{(2)}\) In high-income countries such as Australia, France, Canada, the United Kingdom (UK) and the United States of America (USA) there has been an increased incidence of primary atonic PPH in the last 10-20 years.\(^{(3, 6-9)}\) However, this increase is not fully explained with changes in known risk factors or reporting.\(^{(3)}\)

One intervention that is anecdotally considered a potential risk factor for primary PPH is the administration of intravenous (IV) fluids during labour. The use of IV fluids as part of labour care is common in high-income countries such as Australia, Canada, and the USA.\(^{(10-14)}\) It is biologically plausible a potential relationship exists whereby larger volumes of IV fluids could impair uterine contractility through the development of uterine swelling (15) and/or metabolic acidosis.\(^{(16)}\) Additionally, dilution of clotting factors (coagulopathy)\(^{(16)}\) or endogenous oxytocin could be possible mechanisms. If true, these could contribute to atonic PPH by inhibiting the myometrium from efficiently contracting onto exposed blood vessels after placental separation and/or preventing blood to clot effectively.

The aim of this study was to investigate whether there is a relationship between the administration of IV fluids during labour and primary PPH. The primary objective was to evaluate whether the administration of high-volume IV fluids during labour \( (\geq 2500 \text{ mL}) \) increases the risk of primary PPH for women with a term gestation, singleton pregnancy, in comparison to low-volume IV fluids during labour \( (<2500 \text{ mL}) \).

2.0 Methods

2.1 Study design

This was a single-site retrospective cohort study. The study factor was exposure to IV fluids during labour and the primary outcome was PPH. This study is reported using STROBE guidelines.\(^{(17)}\)

2.2 Participants

All women who birthed at a metropolitan tertiary referral hospital in Sydney, Australia between 1\textsuperscript{st} September 2021 and 31\textsuperscript{st} October 2022 who met the inclusion criteria were eligible for the study. Inclusion criteria were: a live singleton fetus in a cephalic presentation; planned vaginal birth; and admitted for labour and birth care between 37\textsuperscript{+0} weeks and 42\textsuperscript{+0} weeks gestation. Exclusion criteria were: IV fluid data or estimated maternal blood loss documentation insufficient and/or missing. Participants received routine care including the intake of oral fluids and the administration of 10 units oxytocin intramuscularly at birth to prevent PPH, with a second dose if greater than expected blood loss or uterine atony were observed.

2.3 Study variables

Primary PPH was defined as maternal blood loss \( \geq 500 \text{ mL} \) within 24 hours after birth. The data sources included the hospital’s clinical electronic database, electronic medical records and paper fluid order documentation. Maternal estimated blood loss (EBL) was extracted from the hospital’s clinical electronic database.
In cases where EBL was missing from the clinical electronic database, case documentation was reviewed by the lead author to identify the clinician recorded EBL within the written electronic progress notes. The total volume of IV fluids administered was determined by reviewing related documentation within the clinical electronic database, electronic medical records, and paper fluid order documentation. The total volume of IV fluids administered was calculated from the point of first administration during labour to the time of birth. While the complete medical records (electronic and paper fluid order documentation) consistently recorded the total number of bags of fluids prescribed, it was often unclear what proportion of the final bag of fluids had been administered before the time of birth due to unreliable documentation of IV fluid administration rates in the electronic clinical records. Total intrapartum IV fluid volume was therefore manually estimated by determining the duration of time over which the previous bag of fluids was administered, calculating the rate (in mL/hr), and applying this rate to the final bag. In cases where a single bag of IV fluids was administered, the rate could not be determined, and it was assumed that the total bag volume (including the additional volume of any oxytocin) was administered by time of birth.

Secondary outcomes included: Severe primary PPH (defined as maternal blood loss [≥] 1000 mL within 24 hours after birth); atonic PPH; immediate PPH management; blood product transfusion; major perineal injury ([≥] 3rd degree perineal injury); and caesarean section birth. Additionally, variables were collected as co-variates, these included: birth weight; maternal pyrexia ([≥] 38 °C on at least one occasion during labour); intrapartum IV antibiotics for infection; duration of active labour (from the time of regular uterine contractions with the cervix [≥] 4cm dilated to the time of birth); epidural anaesthesia during labour; instrumental birth; emergency caesarean section; genital tract injury; retained placenta/membranes; hypertensive disorders of pregnancy; model of care; body mass index (BMI); and parity. Baseline characteristics and demographic variables were collected in accordance with the Core Outcomes in Women’s and Newborn Health (CROWN) initiative.(18)

2.4 Study sample size

Study sample size was calculated using the odds ratio for multiple logistic regression for a binary outcome using the method described by Hsieh et al.(19) We assumed an alpha value of 0.05, a beta value of 0.2, P1 (rate of PPH in the unexposed group) of 20%, an odds ratio of 1.65 (a relative risk of approximately 1.5), and B (proportion of the population exposed to IV fluid [≥] 2500 mL) = 50%. This gave a required sample size of 686. We then calculated the R2 using data from a previous study(11) to estimate that 32% of the variance in the use of IV fluids was due to the covariates and adjusted the sample size using a variance inflation factor of 1.47 [=1/(1-R2)] to calculate the final required sample size of 1009 participants.

2.5 Statistical analysis

The analysis was performed using the statistical software program SAS version 9.4(20). Descriptive statistics included means and standard deviations for parametric data, medians and interquartile ranges for non-parametric data and percentages for categorical data. Multivariable logistic regression was used to explore the relationship between volume of IV fluids in labour (high volume versus low volume) and estimated maternal blood loss [≥]500 mL. A p value of <0.05 was considered statistically significant. Explanatory variables were determined prior to the analysis based on a review of the current literature. These were: maternal age, BMI, country of origin, parity, model of care, IV antibiotics for infection/suspected infection, type of birth, degree of perineal injury, duration of active labour, and birth weight. Continuous explanatory variables (e.g. maternal age, BMI, and birthweight) were tested for linear association by sorting into clinically relevant groups (e.g., maternal age <25, 25-29, 30-34, and ≥ 35 years) and plotting the beta-coefficients against the midpoints for each group. Variables without linearity were analysed by these groups. Multiple imputation was attended for missing data using 20 iterations. Logistic regression was performed on each of the 20 datasets and summary regression parameters were reported.

2.6 Ethics Approval

Human Research Ethics Committee approval was gained through Sydney Local Health District on the 27th of April 2020 (Protocol No. X19-0430 & 2019/ETH13385).
3.0 Results

A total of 1403 cases were reviewed. After exclusions for insufficient IV fluids documentation, 1023 cases were included in the analysis (Figure 1). The volume of IV fluids administered ranged from 0 mL to 5751 mL. Two types of crystalloid IV fluids were used: 0.9% Normal Saline and Hartmann’s solution (Compound Sodium Lactate). These were administered at variable rates. The low-volume IV fluids group (<2500 mL) included 810 cases, and the high-volume IV fluids group (≥2500 mL) included 213 cases. Maternal demographics and clinical characteristics for the two groups are summarised in Table 1 and Table 2.

3.1 Primary Postpartum Haemorrhage (PPH)

A total of 339 women had a primary PPH (EBL ≥ 500mL) (33.1%), with 252/810 women (31.1%) in the low-volume IV fluids group and 87/213 (40.8%) in the high-volume IV fluids group. Sixty-four (7.9%) in the low-volume group and 24 (11.3%) in the high-volume group had a severe primary PPH (EBL ≥ 1000mL). There was a positive association between high-volume IV fluids and primary PPH ≥ 500 mL in the univariable logistic regression (odds ratio [OR] 1.53 95% confidence interval [CI]: 1.12, 2.09). However, the OR decreased to 1.02 (95% CI: 0.72, 1.44) and statistical significance was not reached in the multiple logistic regression (Table 3).

3.2 Maternal estimated blood loss (EBL)

Maternal estimated blood loss ranged from 40 mL to 3400 mL for the cohort (median 350 mL, IQR 300-600 mL). The median EBL for the low-volume IV fluids group was 350 mL (IQR 250-500 mL) and 400 mL (IQR 300-600 mL) for the high-volume IV fluids group (Wilcoxon rank sum test, p = 0.003).

3.3 Incidence of atonic PPH

Due to insufficient documentation, it was unable to be ascertained retrospectively whether uterine atony was the principal cause of the observed PPHs.

3.4 Immediate PPH management

A majority of the sample (62.2%) were administered a 40 units oxytocin infusion in the postpartum period for either PPH prophylaxis or PPH management: 471/810 (58.1%) in the low-volume IV fluids group and 165/213 (77.5%) in the high-volume IV fluids group. It was not possible to collect the specifics of further medical and/or surgical management of PPH in this retrospective study.

3.5 Postpartum Red Blood Cell Transfusion

A total of fifteen women required a postpartum red blood cell transfusion (1.5%), 11/810 (1.4%) in the low-volume IV fluids group and 4/213 (1.9%) in the high-volume IV fluids group. Additionally, one woman required a repeat red blood cell transfusion the following day in the low-volume IV fluids group. Due to the low number of events, a regression analysis to test for an association with IV fluids administration was not performed.

3.6 Major Perineal injury (≥ 3rd degree perineal injury)

A total of 27 women out of the 745 women who had a vaginal birth (3.6%) sustained a major perineal injury. Due to the low number of events, categorical covariates in the multivariable logistic regression were condensed into fewer categories (Table S1). Parity, country of origin (surrogate for ethnicity), use of forceps and birthweight were included in the model as they are recognised risk factors for obstetric anal sphincter injury. Volume of IV fluids was associated with major perineal injury in the univariable regression (ORunadj 2.5; 95% CI: 1.07, 5.9). However, in the multivariable logistic regression, only the use of forceps was associated with major perineal injury (ORadj 3.0 95% CI: 1.2, 7.6) (Table S1).

3.7 Emergency Caesarean section

Overall, 278 women had an emergency caesarean section (27.2%), 176/810 (21.7%) women in the low-volume IV fluids group, and 102/213 (47.9%) women in the high-volume IV fluids group. The unadjusted logistic
regression showed that women in the high-volume IV fluids group were more likely to have an emergency caesarean section than women in the low-volume IV fluids group (OR_{unadj} 3.3; 95% CI: 2.4, 4.5). In the adjusted model, emergency caesarean section remained associated with high-volume IV fluids after adjusting for maternal age, birth weight, BMI, Intrapartum IV antibiotics for infection/suspected infection, maternal origin, parity, previous caesarean section, length of active labour, and model of care (OR_{adj} 1.99; 95% CI: 1.4, 2.8) (Table S2). Additionally, women born in South-East Asia (OR_{adj} 1.5; 95% CI: 1.008, 2.3), duration of active labour [?] 12 hours (OR_{adj} 1.6; 95% CI: 1.04, 2.5), and neonatal birthweight [?] 4000 grams (OR_{adj} 2.4; 95% CI: 1.3, 4.4) were associated with emergency caesarean section in the adjusted model (Table S2).

4.0 Discussion

4.1 Main Findings

This study did not find an association between high volume IV fluids and PPH after adjusting for demographic and clinical factors. PPH [?] 500 mL was associated with maternal BMI [?] 35, nulliparity, women born in South-East Asia, emergency caesarean birth, and birth weight [?] 4kg. Maternal BMI>35 and duration of active labour [?] 12 hours was associated with PPH [?] 1000 mL after adjusting for confounding factors. These associations were expected and supports the findings of other research exploring risk factors for PPH. (7, 8, 21-23) A second unexpected finding was the positive association between high-volume IV fluids and emergency caesarean section.

4.2 Interpretation

Our study found women were more likely to require an emergency caesarean section if they received [?] 2500 mL IV fluids compared to <2500 mL. This finding is in contrast to Coco et al. (24) and Garite et al.(14) that reported no statistical difference for total caesarean sections in their randomised controlled trials (RCTs) evaluating increased rates of IV fluids to nulliparous women in spontaneous labour. Duffy et al.(13) also reported no statistical difference in caesarean section rates for their more recent RCT examining increased IV hydration in nulliparous women undergoing induction of labour. However, it is important to note that our study included both nulliparous and parous women, in either spontaneous, augmented, or induced labour, and had a much larger sample size than those three RCTs. Similarities included the IV fluid types and the overall total volume administered between intervention and controls, with both Coco et al.(24) and Garite et al.(14) reporting total IV fluids volumes of approximately 2500 mL or greater for their increased IV fluids group. In contrast, Duffy et al.(13) reported much larger mean IV fluids volumes of 3476.8 mL for their 125 mL/hr group and 6984.5 mL for their 250 mL/hr group. PPH was not a reported outcome of Duffy et al.(13)

Whilst our study was not designed to answer the specifics as to why this result may have occurred, it is conceivable that IV fluids in labour may influence the power, passenger, or passage. For example, through increased fetal weight from the transfer of additional IV fluids across the placenta.(25, 26) Additionally, there is biological plausibility that altered uterine contractility related to IV fluids administration could increase the risk of emergency caesarean section.(15) In the work by Moen et al. (27) there was a statistically significant correlation between perinatal hyponatraemia (plasma sodium levels <130 mmol/L) and emergency caesarean section for slow progress in labour. Our results support the need for further prospective research, ideally larger sized RCTs examining the administration of IV fluids in labour and maternal outcomes such as emergency caesarean section for slow progress in labour.

Finally, our observed rates of PPH [?] 500 mL and PPH [?] 1000 mL of 33.1% and 8.6% of births respectively were higher than expected. In 2021, the rate of PPH within Australia was approximately 21%. (28) However, the true rate may be higher, with differences in definitions and reporting methods possibly contributing to underreporting. (6, 7) The rate of PPH in this study was comparable to a UK cohort examined by Briley et al. (7) who reported a 33.7% incidence for PPH [?] 500 mL and 3.9% for PPH [?] 1000 mL. The authors reported that to the best of their knowledge, it was the highest incidence of PPH reported from any high-income or low-income country and concluded that there is a need for policy and research to focus on potentially modifiable risk factors for PPH. (7) This sentiment is echoed by the World Health Organization.
and in Australia, with the prevention and management of primary PPH seen as an area of research priority due to the potential for maternal death and negative long-term health impacts for both mother and baby.\textsuperscript{(29, 30)}

### 4.3 Limitations

The main limitation of this study was inadequate documentation of maternal fluid balance. This limitation has been encountered by other researchers investigating intrapartum IV fluids practices.\textsuperscript{(11, 31, 32)} In our study inadequate documentation necessitated the exclusion of certain cases and the assumption of consistent IV fluids administration rates continued between bags. Whilst this approach helped to mitigate selection bias and uphold the study’s internal validity, there remains the potential that non-differential misclassification of IV fluids volume occurred. Moreover, the necessity to categorise IV fluids intake into two groups may have diluted our findings and increased the risk of a Type 2 error (failing to reject a false null hypothesis).

A second limitation of this study was the visual estimation of maternal blood loss. Maternal blood loss at birth can be underestimated when visual estimation is used.\textsuperscript{(7, 33)} Consequently, maternal blood loss may have been systematically underestimated, particularly given the infrequent documentation of cumulative blood loss within the initial 24 hours postpartum.

### 4.4 Future Research

Currently, a large evidence gap exists regarding the administration of IV fluids during labour and their effects on maternal and neonatal outcomes. Reporting of common practices for IV fluids administration in labour is limited. Addressing this knowledge gap is important for designing future prospective studies that accurately reflect interventions used in clinical practice. Whilst RCTs may be helpful in exploring maternal and neonatal outcomes, without knowing what ‘usual practice’ is, the tested interventions may not reflect current practice, limiting any knowledge gain.

Inadequate documentation of maternal fluid balance is a key barrier to rigorous prospective research in this area due to the imprecise recording of the exposure variable. Considering the potential impact of IV fluids on labour, including disruptions to electrolyte balance and uterine contractility, events such as IV fluid boluses and interruptions in IV infusion may hold considerable importance. Adopting practices that enhance the documentation of maternal fluid balance, such as integrating implementation science methods and frameworks to support health service engagement, identify workflow logistics and promote behaviour change,\textsuperscript{(34-36)} could prove advantageous in future research.

### 5.0 Conclusion

This study found that there was not an association between high volume IV fluids and PPH after adjusting for demographic and clinical factors for this cohort of women at a single, metropolitan, tertiary referral hospital. However, there was a positive association between high-volume IV fluids and emergency caesarean section. Overall, these findings are important to further knowledge relating to the administration of IV fluids in labour and the potential impact of this common practice. It identifies future research priorities around documentation of IV fluids and their relationship with pregnancy and perinatal outcomes.

### 6.0 Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### 7.0 Author Contributions

BB: Conceptualisation, methods, validation, investigation, resources, data curation, data analysis, writing – original draft preparation, writing – review and editing, visualisation, project administration. HS: methods, writing - review and editing, resources, supervision; SK: methods, investigation, resources, writing - review and editing. CH: investigation, writing- review and editing. JL: Conceptualisation, methods, writing -
review and editing, resources, supervision. BdV: Conceptualisation, methods, validation, investigation, data analysis, writing - review and editing, resources, supervision.

8.0 Conflict of Interest

No conflict of interest has been declared by the authors.

9.0 Patient or public consultation

This study was presented at a peer review research meeting at the study site during the planning stages of the study. No other patient or public consultation was attended.

10.0 Acknowledgments

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Figure 1 participant flow chart.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study

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Table 1 Demographic characteristics of 1023 women planning a vaginal birth at 37 or more weeks' gestational age.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study

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Table 2 Clinical characteristics of 1023 planning a vaginal birth at 37 or more weeks gestational age.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study

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Table 3 Multiple imputation and logistic regression for postpartum haemorrhage among 1023 women planning a vaginal birth at 37 or more weeks' gestational age.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study

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Table S1 Multiple imputation and logistic regression for severe perineal injury.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study

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Table S2 Multiple imputation and logistic regression for emergency lscs.docx available at https://authorea.com/users/759217/articles/733655-association-between-intravenous-fluids-during-labour-and-primary-postpartum-haemorrhage-a-retrospective-cohort-study