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Cooling the Lower Abdomen for Preventing Postpartum Hemorrhage :
A Randomized Controlled Trial

14DN013

Yuko Masuzawa

要旨

目的

分娩後出血は妊産婦死亡の主要な原因の1つである。分娩後出血の予防介入方法の中には未だ有効性が検証されていないものも多い。そのひとつである下腹部を冷やすことは、日本で実践されている分娩後出血に対する介入方法で、現在でも関東圏の医療施設の8割で実施されている。本研究は、アイスノン®を置いて下腹部を冷やすことの分娩後出血の予防に対する有効性を検証することを目的とした。

方法

子宮収縮薬の予防投与をルチーンで行っていない首都圏の医療施設1施設にて、ランダム化比較試験を実施した。組入基準は、妊娠34~42週未満の単胎で頭位の児を経膣分娩する予定の女性を対象とした。前置胎盤、1,000ml以上の出血既往や、緊急帝王切開となった場合、分娩第3期に子宮収縮薬の予防投与を受けた場合は除外した。対象者は胎盤娩出時に、下腹部を冷やすことを受ける介入群か、非介入群のどちらかに割り付けられた。介入群は、胎盤娩出後より2時間の間、アイスノン®を用いて下腹部を冷やすことを受けた。本研究のプライマリアウトカムは、分娩後2時間の総出血量とし、セカンダリアウトカムは、500g以上の分娩後出血の発生、1,000g以上の分娩後出血の発生、治療的子宮収縮薬の投与の実施とした。分析はITT解析で2群の比較を行った。聖路加国際大学研究倫理審査委員会において承認を得られた後に実施した(承認番号:15-062)。臨床試験登録を行ったUMIN-CTR(ID:UMIN000019834)。

結果

81名の女性が介入群に、79名の女性が非介入群に割り付けられた。2群の基本特性はほぼ同等であったが、平均分娩第3期出血量は、介入群が452.7g、対照群が396.1gと不均等であった。プライマリアウトカムである平均総出血量は、介入群が513.3g、対照群が478.1gと介入群の方が出血は多かった($p=.49$)。介入実施期間である平均分娩後2時間出血量は、介入群が60.6g、対照群が82.0gと介入群の方がわずかに少なかった($p=.086$)。500g以上の分娩後出血の発生は、介入群が36名(44.4%)、対照群が28名(35.4%)であった($RR\ 1.21, 95\% CI [0.86, 1.7]$)。1,000g以上の分娩後出血の発生は、介入群が6名(7.4%)、対照群が6名(7.6%)と差はなかった($RR\ 0.98, 95\% CI [0.55, 1.78]$)。治療的子宮収縮薬の投与を実施したのは、介入群32名(39.5%)、対照群40名(50.6%)と差はなかった($RR\ 0.79, 95\% CI [0.58, 1.09]$)。

介入群において介入による有害事象(皮膚の発赤や凍傷など)を生じた女性はいなかったが、介入群のうち7名(8.6%)が冷却による不快感を訴え、介入を中止した。

結論

下腹部を冷やすことは、分娩後2時間の総出血量を減らすまでには至らず、効果も小さく、不快感を生じることから、分娩後出血予防を目的とした下腹部を冷やすことの臨床的な意義は小さいと考える。

Abstract

Purpose: Cooling the lower abdomen is one of the Japanese traditional non-pharmacological prophylactic managements for PPH. This study evaluated the effectiveness of cooling the lower abdomen during the first two hours after the placental delivery in reducing postpartum blood loss compared with no intervention.

Methods: This randomized controlled trial was conducted in a medical center in Japan. Eligible women were expecting: (1) a vaginal delivery at the hospital, and those had a (2) singleton pregnancy, (3) cephalic presentation at or more than 34-week gestation and (4) without augmentation of labor or administration of oxytocin in the third stage. They were randomly assigned to the intervention group (cooling the lower abdomen) or control group (no cooling the lower abdomen) at the time of placenta delivery. The primary outcome was the total blood loss within the two hours after the newborn delivery. The secondary outcomes were the incidence of blood loss of 500 g or more, use of therapeutic uterotonics, and pain level. We compared the two groups for outcomes in an intention to treat analysis. The researcher's Institutional Review Board approved the research (No. 15-062). This trial was registered with UMIN-CTR (UMIN000019834).

Results: Between January and May 2016, 160 women were randomly assigned to the intervention group ($n = 81$) or no intervention group ($n = 79$). The primary outcome was not reduced in the cooling compared to no intervention (mean blood loss 513.3 g versus 478.1 g, mean difference 35.2 g, 95% CI [-65.3, 135.7]). No adverse events were reported; but seven (8.7%) women in the intervention group decline to continue cooling the lower abdomen because of discomfort.

Conclusion: Cooling the lower abdomen is one of the unique non-pharmacological prophylactic managements for PPH in Japan, however a few women felt discomfort with cooling and there was no reduction of postpartum blood loss. Cooling the lower abdomen may not be an effective method for reducing post-partum blood loss for the women who deliver in medical facilities.

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Introduction

Background

Postpartum hemorrhage (PPH) is one of the leading cause of maternal mortality (AbouZahr, 2003; Kassebaum et al., 2014). In spite of Japan's low maternal mortality rate, PPH accounts for about 20 % of all cause of maternal death (Mothers' and Children's Health Organization, 2015). As a significant medical threat, effective strategies for the prevention and treatment of PPH are essential to decrease maternal mortality rates worldwide.

After the birth of the neonate and placenta, hemostasis processes are initiated. With the expulsion of the placenta, hemostasis is activated by clotting and fibrinolytic factors in the blood and decreasing the blood flow caused by uterine muscles contractions during which time, the spiral vessels of the uterus are compressed (Cunningham et al, 2014a). If these mechanisms become deregulated for some reason, then uterine atony or coagulation disorders occur, and have been identified as some of the risk factors of PPH (Baldisseri, 2011; Royal College of Obstetricians and Gynaecologists [RCOG], 2009)

Primary guidelines recommend active management of the third stage of labor, in which the main component is administration of uterotonics as the effective prophylactic management for PPH (National Institute for Health and Care Excellence [NICE], 2014; Royal Australian and New Zealand College of Obstetricians and Gynaecologists [RANZCOG], 2011; Society of Obstetricians and Gynaecologists of Canada [SOGC], 2009; World Health Organization [WHO], 2012). Active management is a package of prophylactic interventions that contain the following components: the administration of an uterotonics after delivery; early umbilical cord clamping; controlled cord traction for earlier delivery of the placenta, and sometimes includes uterine massage (WHO, 2012). The effectiveness of some of the prophylactic management strategies for PPH has been evaluated in Cochrane Reviews: active management of the third stage of labor was evaluated compared with expectant management (Begley, Gyte, Devane, McGuire, & Weeks, 2015), use of uterotonic drugs (Hofmeyr, Gülmezoglu, Novikova, & Lawrie, 2013; Liabsuetrakul, Choobun, Peeyanjarassri, & Islam, 2007; McDonald, Abbott, &

Higgins, 2004; Mori, Nardin, Yamamoto, Carroli, & Weeks, 2012; Oladapo, Fawole, Blum, & Abalos, 2012; Oladapo, Okusanya, & Abalos, 2012; Soltani, Hutchon, & Poulouse, 2010; Su, Chong, & Samuel, 2012; Tunçalp, Hofmeyr, & Gülmezoglu, 2012; Westhoff, Cotter, & Tolosa, 2013), use of hemostatic agents (Novikova, Hofmeyr, & Cluver, 2015), and uterine massage (Hofmeyr, Abdel-Aleem, H., & Abdel-Aleem, M., 2013).

However, some of prophylactic interventions for PPH have not been evaluated. Cooling the uterus, through putting an icepack on the women's lower abdomen, is one of the unique non-pharmacological prophylactic strategies for PPH in Japan; the reasoning is that cold compresses may help contract the myometrium and decrease blood loss. Cold therapy causes blood vessels within the smooth muscles to constrict and decrease the blood flow (Harmer, 1957). Furthermore, blood vessels in the skin are affected by cold, resulting in somato-visceral reflex and subsequent vasoconstriction of relevant internal organs (Harmer, 1957).

In a Japanese survey about management during and after the third stage of labor, cooling the lower abdomen was provided in 80% of medical facilities (Kataoka, Nakayama, Yaju, Eto, & Horiuchi, 2015). There was some evidence about cooling the lower abdomen for postpartum blood loss, but was limited to observational studies (Fujita, Manabe, & Morooka, 1994; Matsuoka & Sannomiya, 2002; Osumi & Horiuchi, 2007) or non-randomization studies (Hayashi, Inagaki, Morita, Mano, & Amano, 1995; Hondo, Ishizuka, & Kikuchi, 1993; Otsuka et al., 1990; Sato, Noro, & Nakayama, 1984), and the findings were the opposite. Many facilities provided cooling the lower abdomen for preventing PPH, but the effect of cooling the lower abdomen for prevention of PPH has not been evaluated.

Purpose of This Study

The aim of this study was to evaluate cooling the lower abdomen during the first two hours after the placental delivery to reduce postpartum blood loss compared with no intervention.

Definition of Postpartum Hemorrhage in This Study

PPH is defined as blood loss of 500 ml or more within the first 24 hours after

delivery (WHO, 2012) or blood loss of 500ml or more during puerperium (American College of Obstetricians and Gynecologists [ACOG], 2006; RANZCOG, 2011).

The definition of PPH was categorized by the timing of occurrence and the amount of blood loss. Primary PPH is defined as abnormal bleeding within the first 24 hours of delivery, and secondary PPH is excessive bleeding that occurs from the 24 hours until 12 weeks after delivery (Baldisseri, 2011; RCOG, 2009). PPH is further sorted by amount into minor PPH (500 to 1,000 ml) or major PPH (more than 1,000 ml). Furthermore, major PPH is divided into moderate (1,000 to 2,000 ml) or severe, which is more than 2,000 ml (RCOG, 2009). A WHO definition state that, severe PPH is defined to blood loss of 1,000 ml or more within 24 hours after birth (WHO, 2012). The definition of PPH varies, there are some opinions that PPH is defined as the blood loss of 1,000 ml or more because of the clinical significance (AbouZahr, 2003).

In the Japanese Obstetrical Clinical Guideline, the blood loss of 500 ml or more is suspected as excessive bleeding after childbirth (Japan Society of Obstetrics and Gynecology & Japan Association of Obstetricians and Gynecologists, 2014). According to the glossary of obstetrics which was published by the Japan Society of Obstetrics and Gynecology, in case of the total amount of blood loss within the first two hours after delivery, blood loss over 500 ml, it is defined as abnormal bleeding (Japan Society of Obstetrics and Gynecology, 2013). Because of these variations in definitions, the definition of PPH in this study was the total blood loss of 500ml or more within the first two hours after the delivery.

Literature Review

This section describes the extant literature about PPH, hemostasis process after delivery and how to manage the cooling intervention for PPH. The prophylactic management for PPH and the effectiveness were described in preliminary studies section.

Incidence of Postpartum Hemorrhage

The incidence of PPH (blood loss \geq 500 ml) is around 6 to 10% and, the prevalence of severe PPH (blood loss \geq 1,000 ml) is approximately 1.8%, but it varies depending on the regions of the world (Carroli, Cuesta, Abalos, & Gulmezoglu, 2008). PPH accounted for 19.7% (95% uncertainty interval (UI) [12.9, 28.9]) of the direct causes of maternal death worldwide (Say et al., 2014). Even in Japan, a country exhibiting low maternal mortality rates of about 3.4 per 100,000 live births in 2013, PPH was one of the major causes (20%) of maternity death (Mothers' and Children's Health Organization, 2015).

Hemostasis Process and How to Work the Cooling

After the birth of the neonate and placenta, two hemostasis processes are initiated. The primary physiology of postpartum hemostasis involves uterine muscular contractions induced by endogenous oxytocin and prostaglandins. The structure of uterine smooth muscle is spiral in shape and extends in all directions. When the uterine muscles contract, the spiral vessels of the uterus are compressed, and blood flow decreases (Khan & El-Rafaey, 2012). Retraction of the muscle assures that the contracted state remains. Moreover, clotting and fibrinolytic factors in the blood of pregnant women increase (Burbank, 2012). The concentrations of all clotting factors, fibrinogen, factor VII, factor X and plasminogen, except for factors IV and VIII, increase during normal pregnancy. Likewise, fibrinogen concentration increases about 50 percent. The platelets also change; the average blood platelet count decreases to 213,000/ μ L during pregnancy, but retains the balance of hemostasis (Cunningham et al, 2014a). During the third stage of labor the clotting and fibrinogen factors should return to normal supporting the hemostasis process (Burbank, 2012).

Blood vessels in the skin are affected by cold, resulting in somato-visceral

reflex and subsequent vasoconstriction of relevant internal organs (Harmer, 1957). The pelvic viscera are controlled by sympathetic nerve fibers from thoracic 10 to lumbar 2 and parasympathetic fibers of sacral 2 to sacral 4 (Cunningham et al, 2014b). Cold therapy on the lower abdomen and the somato-visceral reflex decreases the blood flow of the uterus which is an organ in a women's pelvis; thus, cooling the uterus could prevent PPH.

The Causes Leading to Postpartum Hemorrhage

Events that may influence PPH include uterine atony, cervical or vaginal lacerations, retention of the placenta, and coagulation disorders (Baldisseri, 2011; RCOG, 2009). Among these, the most prominent cause of PPH is uterine atony (34.0%) (Ford, Shand, & Roberts, 2013).

The Risk Factors for Postpartum Hemorrhage

Maternal factors. Age \geq 35 years (Sheldon et al., 2014), body mass index (BMI) \geq 30 kg/m² (Fyfe, Thompson, Anderson, Groom, & McCowan, 2012), Pacific island or Asian ethnicity (Combs, Murphy, & Laros, 1991; Fyfe et al., 2012), parity of three or more (Sheldon et al., 2014); primiparas (Combs et al., 1991; Ford et al., 2013; Magann et al., 2013), multiple births (Combs et al., 1991; Ford et al., 2013; Suzuki, Hiraizumi, & Miyake, 2012), history of PPH (Combs et al., 1991), hypertensive disorders (Fyfe et al., 2012), pre-eclampsia (Combs et al., 1991; Fyfe et al., 2012).

Abnormal placentation. Abnormal placentation is a group of placental attachment disorders. They include placenta previa (Fyfe et al., 2012; Suzuki et al., 2012), placental abruption (Suzuki et al., 2012), and retained placenta (Magann et al., 2013).

Obstetrical factors. Numerous events associated with labor and deliver lead to PPH. These events are: induction of labor (Combs et al., 1991; Fyfe et al., 2012; Sheldon et al., 2014), prolonged labor (Combs et al., 1991; Ford et al., 2013; Magann et al., 2013), obstructed labor (Ford et al., 2013), episiotomy (Combs et al., 1991; Fyfe et al., 2012), instrumental labor (Combs et al., 1991; Fyfe et al., 2012), caesarean section (Sheldon et al., 2014) and gestation age at delivery of $<$ 37 weeks (Sheldon et al., 2014; Suzuki et al., 2012).

Previous Studies about Cooling the Lower Abdomen for Prevention of Postpartum Hemorrhage

There were only seven studies all from Japan researchers that explored the effect of cooling the lower abdomen to reduce the postpartum blood loss. Among the seven studies, four were non-randomized trials (Hayashi et al., 1995; Hondo et al., 1993; Otsuka et al., 1990; Sato et al., 1984), and three were observational studies (Fujita et al., 1994; Matsuoka & Sannomiya, 2002; Osumi & Horiuchi, 2007). The majority of participants delivered vaginally and received prophylactic uterotonics in the third stage of labor (Fujita et al., 1994; Hayashi et al., 1995; Hondo et al., 1993; Matsuoka & Sannomiya, 2002; Otsuka et al., 1990; Sato et al., 1984), in one, study participants used nipple stimulation during the third stage of labor (Osumi & Horiuchi, 2007).

In the intervention studies, the procedures were cooling the lower abdomen during the first two hours after the placental delivery (Hayashi et al., 1995; Hondo et al., 1993; Otsuka et al., 1990; Sato et al., 1984). In the observational studies, participants received cooling during the first two hours of the neonatal delivery (Matsuoka & Sannomiya, 2002; Osumi & Horiuchi, 2007).

The primary outcomes of six studies was the amount of total blood loss during the third stage of labor and the first two hours after the delivery of the placenta (Fujita et al., 1994; Hondo et al., 1993; Matsuoka & Sannomiya, 2002; Osumi & Horiuchi, 2007; Otsuka et al., 1990; Sato et al., 1984). The findings of these studies were opposite; two studies showed cooling reduced the blood loss (Hayashi et al., 1995; Sato et al., 1984), and the other, two studies found that cooling had no effect on the reduction of blood loss (Hondo et al., 1993; Otsuka et al., 1990).

The methods of measuring the amount of blood loss during the third stage of labor of one study (Osumi & Horiuchi, 2007), putting the mat under the maternal buttocks just after delivery of the neonate in order to absorb the amniotic fluid; another study collected the blood loss using a basin under the maternal buttocks (Hayashi et al., 1995). In two studies, sanitary pads were used for measuring the blood loss during the first two hours after the placental delivery (Hayashi et al., 1995; Osumi & Horiuchi, 2007).

In conclusion, there were no studies of participants having no prophylactic

management in the third stage of labor. In order to evaluate the effectiveness of cooling the lower abdomen for preventing PPH only, the participants must include women with no prophylactic strategy during the third-stage. Furthermore, a design that eliminates confounding and bias, and one that identifies the study's outcome measures should be used. Putting the mat under the maternal buttocks just after the newborn delivery is a feasible method for measuring the amount of blood loss during the third stage of labor, because it is possible to place the mat under the maternal buttocks in any maternal birth position.

Preliminary Studies

Study 1. Prophylactic Management for Postpartum Hemorrhage: An Overview of Systematic Reviews

Introduction

Given that PPH usually occurs during and after the third stage of labor (Carroli et al., 2008). The effectiveness of some prophylactic management for PPH in the third stage of labor has been evaluated in Cochrane Reviews. Active management of the third stage of labor was evaluated compared with expectant management (Begley et al., 2015). It is thought that early cord clamping and controlled cord traction as one of the components of active management prevent retained placenta and prevention of a prolonged third stage of labor. Other prophylactic interventions were considered: use of uterotonic drugs, use of hemostatic agents, and uterine massage. For uterotonic drugs, as augmentation of uterine contractions the following were considered: oxytocin (McDonald et al., 2004; Mori et al., 2012; Oladapo, Okusanya, et al., 2012; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013), prostaglandin (Hofmeyr, Gülmezoglu et al., 2013; Oladapo, Fawole, et al, 2012; Tunçalp et al., 2012) and ergot alkaloid (Liabsuetrakul et al., 2007). A survey about using the prophylactic uterotonic agents in 28 countries noted that 95.3% of deliveries used prophylactic uterotonics for preventing PPH and the most used uterotonic agent was oxytocin (Sheldon et al., 2014).

The extant systematic reviews of evidence from randomized controlled trials regarding prophylactic management for PPH has never been summarized and there are several different interventions for PPH prevention presented in separate Cochrane Intervention reviews. Therefore, the objective of this systematic review is to summarize the evidence from systematic reviews regarding the effects of prophylactic management for PPH.

Methods

This overview of systematic reviews applied the guidelines for overview of reviews in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011).

Criteria for Considering Included Review

In this systematic review, I included published systematic reviews of randomized controlled trials in which the prophylactic management for PPH was given to women after delivery. Prophylactic management for PPH includes active management of the third stage of labor, use of uterotonics (oxytocin, prostaglandin, ergot alkaloids), early umbilical cord clamping, controlled cord traction, use of tranexamic acid, and uterine massage. I compared these interventions with placebo, no treatment, intervention in contrast or a different intervention. I searched for the six proposed critical outcomes in the WHO Recommendations for the Prevention and Treatment of Postpartum Hemorrhage Guidelines (WHO, 2012): maternal mortality, blood loss more than 1,000 ml, the use of blood transfusion, blood loss more than 500 ml, using therapeutic uterotonics and mean maternal blood loss.

Search Strategy

A comprehensive search was conducted for relevant published reviews in any language in MEDLINE (via EBSCO, 04 August 2015), EMBASE (1980 to 04 August 2015), Cochrane Database of Systematic Reviews (Issue 8 of 12, August 2015) and Database of Abstracts of Reviews of Effect (Cochrane Library Issue 2 of 4, April 2015), using the search terms *postpartum hemorrhage* and *prevention*. Systematic reviews searching filters in Clinical Evidence (Clinical Evidence, 2012) were used for searching on MEDLINE and EMBASE.

Selection of Systematic Reviews

First, the author assessed all the potential systematic reviews for inclusion resulting from my search strategy. Then, full-text articles were assessed for inclusion.

Data Extraction

A predefined form was used for extracting the data that included: study design, participants, experimental intervention, comparison intervention, outcomes, quality of the review, and pooled effect sizes for main outcome measures meta-analyzed. When the included review did not present the number of outcome events or was meta-analyzed, I checked the individual studies of reviews and then meta-analyzed.

Quality of Evidence in Included Reviews

Quality of evidence in included reviews was examined using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2008) for outcomes. The GRADE approach is the system for evaluating the quality of evidence, assessed as four levels (very low, low, moderate and high) of five domains: 1) study limitations, 2) inconsistency of results, 3) indirectness of evidence, 4) imprecision, and 5) publication bias (Guyatt et al., 2008). We used the GRADEPro software 'summary of findings' tables for each outcome.

Assessment of Methodological Quality of Included Reviews

The quality of evidence and the methodological quality of included reviews were assessed using the instrument: A Measurement Tool to Assess Reviews (AMSTAR) (Shea et al., 2007). The AMSTAR tool assesses 11 criteria (Table 1) and the researcher rated yes, no, cannot answer, or not applicable.

Table 1

Criteria of AMSTAR Tool (Shea et al., 2007)

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Data Synthesis

The author provided a narrative summary of the individual review results for each outcome displayed on tables and figures that include characteristics of each review, AMSTAR ratings and outcomes using GRADE.

Results

Description of Included Reviews

A total of 1,465 studies were identified from the database search. After removing duplicates, 1,377 studies remained. A total of 1,313 titles and abstracts were assessed and removed because they were not systematic reviews or were not about prophylactic management for PPH. There were 64 full texts studies remaining; of those, 38 studies were excluded because they did not include prophylactic management, or were not systematic reviews of randomized controlled trials, or were only abstracts. Finally, 28 studies met inclusion criteria. Figure 1 shows a flow diagram of the selection

process.

Of the 28 systematic reviews, 17 Cochrane systematic reviews and 11 non-Cochrane systematic reviews were analyzed as follows: six studies about active management of the third stage of labor (Begley et al., 2015; Du, Ye, & Zheng, 2014; Fahy, 2009; Hofmeyr, Mshweshwe, & Gülmezoglu, 2015; McCormick, Sanghvi, Kinzie, & McIntosh, 2002; Peña-Martí & Comunián-Carrasco, 2007), seven studies about oxytocin (Jin, Du, Zhang, F., Zhang, K., Wang, & Cui, 2016; McDonald et al., 2004; Mori et al., 2012; Oladapo, Okusanya, et al., 2012; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013), seven studies about prostaglandin (Hofmeyr, Gülmezoglu, et al., 2013; Hofmeyr et al., 2009; Joy, Sanchez-Ramos, & Kaunitz, 2003; Langenbach, 2006; Oladapo, Fawole, et al., 2012; Olefile, Khondowe, & M'rithaa, 2013; Tunçalp et al., 2012), one study about ergot alkaloids (Liabsuetrakul et al., 2007), four studies about tranexamic acid (Faraoni, Carlier, Samama, Levy, & Ducloy-Bouthors, 2014; Ferrer, Roberts, Sydenham, Blackhall, & Shakur, 2009; Heesen et al., 2014; Novikova et al., 2015), one study about timing of umbilical cord clamping (McDonald, Middleton, Dowswell, & Morris, 2013), one study about uterine massage (Hofmeyr, Abdel-Aleem, et al., 2013) and prophylactic management during postpartum period (Yaju, Kataoka, Eto, Horiuchi, & Mori, 2013). The participants in these reviews had caesarean or vaginal deliveries. Table 2 shows the characteristics of these reviews.

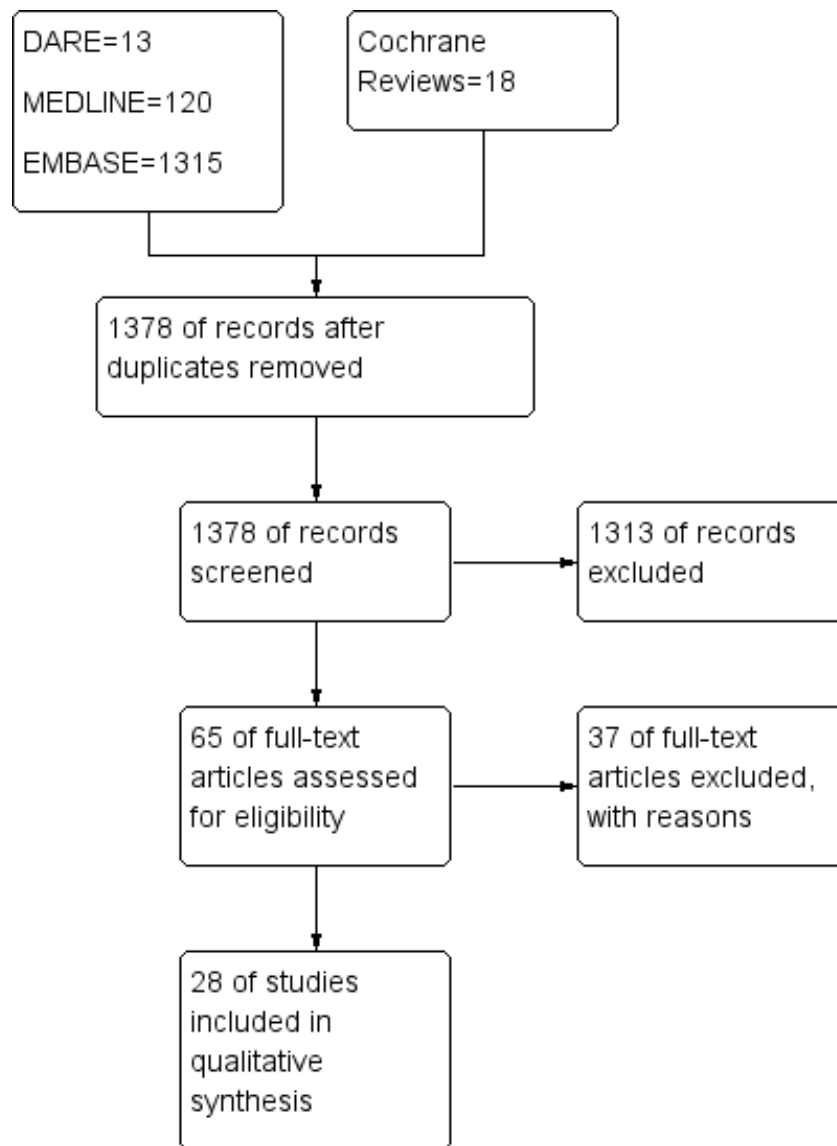


Figure1. Study flow diagram.

Table 2
Included Systematic Reviews

Review title	Date of search	No. Studies included	Population	Intervention	Comparison intervention	Outcomes for which data were reported
Active management						
Cochrane review						
Fundal pressure versus controlled cord traction as part of the active management of the third stage of labor (Peña-Martí, 2007)	August 2010	No RCTs	N/A	Fundal pressure with routine administration of a uterotonic drug and early cord clamping	Controlled cord traction with routine administration of a uterotonic drug and early cord clamping	Empty Review
Active versus expectant management for women in the third stage of labor (Begley, 2015)	30 September 2014	7 RCTs	8,247 women	Active management of the third stage of labor	Expectant management of the third stage of labor	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Controlled cord traction for the third stage of labor (Hofmeyr, 2015)	29 January 2014	3 RCTs	28,049 women	Controlled cord traction with uterotonics	No controlled cord traction with uterotonics	<ul style="list-style-type: none"> • Maternal death • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Non-Cochrane review						
Preventing postpartum hemorrhage in low-resource settings (McCormick, 2002)	September 2001	3 RCTs	4,855 women	Active management of the third stage of labor	Physiologic management	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics
Third Stage of Labor Care for Women at Low Risk of Postpartum Hemorrhage (Fahy, 2009)	February and August 2008	No RCTs	N/A	Active management	Expectant Physiologic management	Empty Review
Active management of the third stage of labor with and without controlled cord traction: A systematic review and meta-analysis of randomized controlled trials. (Du, 2014)	30 October 2013	5 RCTs	30,532 women	Controlled cord traction	Hands-off Physiological expulsion of placenta	<ul style="list-style-type: none"> • Maternal death • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics
Pharmacological management (Oxytocin)						
Cochrane review						
Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labor. (McDonald, 2004)	30 April 2007	6 RCTs	9,332 women	Ergometrin-oxytocin	Oxytocin	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics
Timing of prophylactic uterotonics for the third stage of labor after vaginal birth. (Soltani, 2010)	September 2009	3 RCTs	1,671 women	Intramuscularly or Infusion of oxytocin (10 or 20 units), at delivery of the baby's anterior shoulder or after the 2nd stage of labor	Intramuscularly or Infusion of oxytocin (10 or 20 units), after the birth of placenta.	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Umbilical vein injection for the routine management of third stage of labor. (Mori, 2012)	31 January 2012	9 RCTs	1,118 women	Normal saline or uterotonic drugs, or both, via the umbilical cord	Other alternatives (similar agents IV or IM or no injection/placebo)	<ul style="list-style-type: none"> • Maternal blood transfusion • Mean maternal blood loss
Intramuscular versus intravenous prophylactic oxytocin for the third stage of labor. (Oladapo, 2012)	31 December 2011	No RCTs	N/A	Intramuscular oxytocin	Intravenous oxytocin	Empty Review
Carbetocin for preventing postpartum hemorrhage. (Su, 2012)	1 March 2011	11 RCTs	2,635 women	Oxytocin agonist (carbetocin)	Other uterotonic agents or with placebo or no treatment	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Prophylactic oxytocin for the third stage of labor to prevent postpartum hemorrhage. (Westhoff 2013)	31 May 2013	20 RCTs	10,806 women	Prophylactic oxytocin oxytocin plus ergometrine	Placebo ergot alkaloids ergot alkaloids	<ul style="list-style-type: none"> • Maternal death • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Non-Cochrane review						
Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. (Jin, 2016)	September 2013	12 RCTs	2,975 women	carbetocin	Other uterotonic agents	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • Therapeutic uterotonics • Mean maternal blood loss

Table 2
Included Systematic Reviews (Continued)

Pharmacological management (Prostaglandin)						
Cochrane review						
Advance misoprostol distribution for preventing and treating postpartum hemorrhage. (Oladapo, 2012)	5 October 2011	No RCTs	N/A	Advance misoprostol distribution	Usual care for PPH prevention or treatment	Empty Review
Prostaglandins for preventing postpartum hemorrhage. (Tunçalp, 2012)	7 January 2011	72 RCTs	52,678 women	Prostaglandin agent in the third stage of labor	Another uterotonic or no prophylactic uterotonic (nothing or placebo)	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Postpartum misoprostol for preventing maternal mortality and morbidity. (Hofmeyr, 2013)	11 January 2013	78 RCTs	59,216 women	Misoprostol	Placebo/no treatment or other uterotonics	<ul style="list-style-type: none"> • Maternal death
Non-Cochrane review						
Misoprostol use during the third stage of labor (Joy, 2003)	January 1996 to May 2002	17 RCTs	28,170 women	Misoprostol	Placebo or other uterotonics	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • PPH (≥ 500 ml) • Therapeutic uterotonics
Misoprostol in preventing postpartum hemorrhage: a meta-analysis (Langenbach, 2006)	May 2005	22 RCTs	30,017 women	Misoprostol	Placebo or oxytocics	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • PPH (≥ 500 ml) • Therapeutic uterotonics
Misoprostol to prevent and treat postpartum hemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects (Hofmeyr, 2009)	February 2007	46 RCTs	more than 40,000 women	Misoprostol	Placebo / other uterotonics	<ul style="list-style-type: none"> • Maternal death • Severe PPH (≥ 1000 ml) • PPH (≥ 500 ml)
Misoprostol for prevention and treatment of postpartum hemorrhage: a systematic review (Olefile, 2013)	Unclear	3 RCTs	2,346 women	Misoprostol compared	Placebo for the prevention and treatment of PPH	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Pharmacological management (Ergot alkaloid)						
Cochrane review						
Prophylactic use of ergot alkaloids in the third stage of labor. (Liabsuetrakul, 2007)	30 April 2011	6 RCTs	1,996 women	Any ergot alkaloid given prophylactically, by whatever route or timing of administration	No uterotonic agents	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Pharmacological management (Tranexamic acid)						
Cochrane review						
Tranexamic acid for preventing postpartum hemorrhage. (Novikova, 2015)	28 January 2015	12 RCTs	3,285 women	Trenaxamic acid	Placebo or other agents such as uterotonics	<ul style="list-style-type: none"> • Maternal death • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Mean maternal blood loss
Non-Cochrane review						
Anti-fibrinolytic agents in postpartum hemorrhage: a systematic review (Ferrer, 2009)	November 2008	3 RCTs	461 women	Tranexamic acid	No treatment	<ul style="list-style-type: none"> • PPH (≥ 500 ml) • Mean maternal blood loss
Efficacy and safety of tranexamic acid administration for the prevention and/or the treatment of post-partum hemorrhage: A systematic review with meta-analysis (Faraoni, 2014)	Unclear (French)	10 RCTs	3,014 women	Tranexamic acid	Placebo	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Prophylactic tranexamic acid in parturients at low risk for post-partum hemorrhage: Systematic review and meta-analysis (Heesen, 2014)	10 May 2013	7 RCTs	1,760 women	Tranexamic acid	Placebo	<ul style="list-style-type: none"> • Maternal blood transfusion • PPH (≥ 500 ml) • Mean maternal blood loss

Table 2
Included Systematic Reviews (Continued)

Non-Pharmacological management						
Cochrane review						
Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. (McDonald 2013)	13 February 2013	15 RCTs	3,911 women	Early cord clamping	Later (delayed) cord clamping	<ul style="list-style-type: none"> • Severe PPH (≥ 1000 ml) • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Uterine massage for preventing postpartum hemorrhage. (Hofmeyr, 2013)	30 April 2013	2 RCTs	1,964 women	Uterine massage commencing after birth of the baby, before or after delivery of the placenta, or both	No intervention or a 'dummy' procedure	<ul style="list-style-type: none"> • Maternal blood transfusion • PPH (≥ 500 ml) • Therapeutic uterotonics • Mean maternal blood loss
Prophylactic management after placental delivery						
Cochrane review						
Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period (Yaju, 2013)	30 April 2013	5 RCTs	1,466 women	Oral methylergometrine	Placebo or no treatment	<ul style="list-style-type: none"> • PPH (≥ 500 ml)

Quality of Included Reviews

The author rated the quality of the systematic reviews using the AMSTAR tool (Shea et al., 2007). The methodological quality of 17 Cochran systematic reviews was high, with scores ranging from 10 to 11. The 11 non-Cochrane systematic review scores varied, from 1 to 7. The majority of the non-Cochrane review did not list the included and excluded studies, and did not consider the quality of included studies.

Quality of Evidence in Included Reviews

The researcher assessed the quality of the evidence of outcomes in the reviews using the GRADE approach. The quality of the evidence varied by reviews. The risk of bias scores or imprecision was serious, therefore the quality of the evidence was low to moderate.

Effect of Interventions

In this review, the details of effect of prostaglandin was not described because prostaglandins are rarely used in Japanese clinical settings.

Effect of interventions for maternal mortality. Five reviews were identified; there were two studies about active management of the third stage of labor

(Du et al., 2014; Hofmeyr et al., 2015), and three studies about use of prostaglandins (Hofmeyr et al., 2009; Tunçalp et al., 2012; Hofmeyr, Gülmezoglu, et al., 2013).

Active management versus contrasting management. For the compared active management in the third stage of labor with controlled cord traction versus without controlled cord traction, there was not a significant difference between groups, relative risk (*RR*) 1.55, 95% Confidence interval (*CI*) [0.88, 2.72], 1 RCT, 23,232 women (Du et al., 2014); *RR* 1.22, 95% *CI* [0.55, 2.74], 2 RCTs, 27,300 women (Hofmeyr et al., 2015).

Effect of interventions for blood loss more than 1,000 ml. A total of 18 reviews were identified; four studies about active management of the third stage of labor (McCormick et al., 2002; Du et al., 2014; Begley et al., 2015; Hofmeyr et al., 2015), five studies about use of oxytocin (McDonald et al., 2004; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013; Jin et al., 2016), four studies about use of prostaglandins (Joy et al., 2003; Langenbach, 2006; Hofmeyr et al., 2009; Tunçalp et al., 2012), one study about ergot alkaloids (Liabsuetrakul et al., 2007), two studies about use of tranexamic acid (Faraoni et al., 2014; Novikova et al., 2015), one study about timing of clamping umbilical cord (McDonald et al., 2013) and one study about uterine massage (Hofmeyr, Abdel-Aleem, et al., 2013). This review described only interventions that compared the intervention with placebo or contrasting management.

Active management versus contrasting management. Compared with physiological or expectant management, active management showed significantly reduction in severe PPH, *RR* 0.36, 95% *CI* [0.23, 0.57], 3 RCTs, 4,855 women (McCormick et al., 2002); average *RR* 0.34, 95% *CI* [0.14, 0.87], 3 RCTs, 4,636 women (Begley et al., 2015). For the comparison of active management in the third stage of labor with controlled cord traction versus without controlled cord traction, there was no significant difference between groups, *RR* 0.91, 95% *CI* [0.77, 1.08], 3 RCTs, 27,454 women (Du et al., 2014); *RR* 0.91, 95% *CI* [0.77, 1.08], 3 RCTs, 27,454 women (Hofmeyr et al., 2015).

Oxytocin versus placebo. Prophylactic use of oxytocin showed a significant reduction in severe PPH compared with placebo, *RR* 0.62, 95% CI [0.44, 0.87], 5 RCTs, 4,162 women (Westhoff et al., 2013). Administration of oxytocin before the delivery of the placenta or after does not significantly alter the incidence of severe PPH, *RR* 0.98, 95% CI [0.48, 1.98], 1 RCT, 130 women (Soltani et al., 2010).

Ergot alkaloids versus placebo. There was no significance between groups comparing oral or intravenous ergot alkaloids with no uterotonics, *RR* 0.32, 95% CI [0.04, 2.59]; 2 RCTs, 1,718 women (Liabsuetrakul et al., 2007).

Tranexamic acid versus placebo. Tranexamic acids significantly reduced the incidence of severe PPH compared with placebo or no treatment *RR* 0.49, 95% CI [0.33, 0.74], 4 RCTs, 1,754 women (Faraoni et al., 2014); *RR* 0.40, 95% CI [0.23 to 0.71], 6 RCTs, 2,093 women (Novikova et al., 2015).

Early versus late cord clamping. There was no significant difference between the groups early cord clamping compared with late clamping, *RR* 1.04, 95% CI [0.65, 1.65], 5 RCTs, 2,066 women (McDonald et al., 2013).

Uterine massage versus no uterine massage. There was no significant difference between the groups implementing uterine massage before placental delivery and no massage, *RR* 2.96, 95% CI [0.31, 28.35], 2 RCTs, 1,291 women (Hofmeyr, Abdel-Aleem, et al., 2013).

Effect of interventions using blood transfusion. This review included 17 reviews with blood transfusion as an intervention; there were four studies about active management of the third stage of labor (McCormick et al., 2002; Du et al., 2014; Begley et al., 2015; Hofmeyr et al., 2015), six studies about use of oxytocin (McDonald et al., 2004; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013; Mori et al., 2012; Jin et al., 2016), two studies about prostaglandin (Tunçalp et al., 2012; Olefile et al., 2013), one study about ergot alkaloids (Liabsuetrakul et al., 2007), two studies about tranexamic acid (Heesen et al., 2014; Novikova et al., 2015), one study about timing of the cord clamping (McDonald et al., 2013) and one study about uterine massage

(Hofmeyr, Abdel-Aleem, et al., 2013). The current study described interventions only compared with placebo or contrasting management in this outcome.

Active management versus contrasting management. Active management of the third stage of labor significantly reduce the use of blood transfusions compared with physiological management or expectant management, *RR* 0.32, 95% *CI* [0.20, 0.51], 3 RCTs, 4,855 women (McCormick et al., 2002); *RR* 0.35, 95% *CI* [0.22, 0.55], 4 RCTs, 4,829 women (Begley et al., 2015). There was no significant difference between the groups for active management with controlled cord traction and without controlled cord traction, *RR* 0.96, 95% *CI* [0.69, 1.33], 3 RCTs, 28,062 women (Du et al., 2014); *RR* 0.94, 95% *CI* [0.68, 1.32], 2 RCT, 27,662 women (Hofmeyr et al., 2015).

Oxytocin versus placebo. There was no significance between groups that compared: oxytocin with placebo, *RR* 0.89, 95% *CI* [0.44, 1.78], 3 RCTs, 3,120 women (Westhoff et al., 2013); administration of oxytocin before delivery of the placenta with after delivery of the placenta, *RR* 0.79, 95% *CI* [0.23, 2.73], 3 RCTs, 1,667 women (Soltani et al., 2010) and that compared umbilical vein injection of a saline with oxytocin with a saline alone, *RR* 3.32, 95% *CI* [0.14, 78.97], 1 RCT, 78 women (Mori et al., 2012).

Ergot alkaloids versus placebo. There was no statistical difference in need for blood transfusion between the ergot alkaloids and no uterotonics groups, *RR* 0.33, 95% *CI* [0.08, 1.40], 3 RCTs, 1,868 women (Liabsuetrakul et al., 2007).

Tranexamic acid versus placebo. Tranexamic acid significantly reduced the incidence of blood transfusion compared with placebo, *RR* 0.34, 95% *CI* [0.20, 0.60], 6 RCTs, 1,662 women (Heesen et al., 2014); *RR* 0.24, 95% *CI* [0.11, 0.53], 6 RCTs, 1,698 women (Novikova et al., 2015).

Early versus late cord clamping. No difference was demonstrated in the need for blood transfusion when the early cord clamping was compared with late cord clamping, *RR* 1.02, 95% *CI* [0.44, 2.37], 3 RCTs, 1,345 women (McDonald et al., 2013).

Uterine massage versus no uterine massage. There was no significance between groups; comparing uterine massage before placental delivery with no massage, *RR* 0.97, 95% CI [0.26, 3.58], 2 RCTs, 1,257 women (Hofmeyr, Abdel-Aleem, et al., 2013), and comparing uterine massage before and after placental delivery with no massage, *RR* 0.97, 95% CI [0.26, 3.58], 3 RCTs, 1,457 women (Hofmeyr, Abdel-Aleem, et al., 2013).

Effect of interventions for blood loss more than 500 ml. A total of 20 reviews were identified; four studies about active management of the third stage of labor (Begley et al., 2015; Du et al., 2014; Hofmeyr et al., 2015; McCormick et al., 2002), five studies about use of oxytocin (Jin et al., 2016; McDonald et al., 2004; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013), four studies about use of prostaglandins (Joy et al., 2003; Langenbach, 2006; Olefile et al., 2013; Tunçalp et al., 2012), one study about ergot alkaloids (Liabsuetrakul et al., 2007), three studies about use of tranexamic acid (Ferrer et al., 2009; Heesen et al., 2014; Novikova et al., 2015), one study about the timing of umbilical cord clamping (McDonald et al., 2013), one study about uterine massage (Hofmeyr, Abdel-Aleem, et al., 2013) and one study about prophylactic management during the postpartum period (Yaju et al., 2013). The following section describes only interventions that were compared to interventions with placebos or contrasting management.

Active management versus contrasting management. Compared with physiological or expectant management, active management two researchers found significant reductions in PPH, *RR* 0.41, 95% CI [0.34, 0.49], 3 RCTs, 4,855 women, (McCormick et al., 2002); average *RR* 0.34, 95% CI [0.27, 0.44], 3 RCTs, 4,636 women (Begley et al., 2015). For the comparison of controlled cord traction versus without controlled cord traction, two researchers found significant reductions in PPH using controlled cord traction, *RR* 0.93, 95% CI [0.87, 0.99], 5 RCTs, 29,037 women (Du et al., 2014); *RR* 0.93, 95% CI [0.88, 0.99], 3 RCTs, 27,454 women (Hofmeyr et al., 2015).

Oxytocin versus placebo. Prophylactic use of oxytocin showed a significant reduction in PPH compared with using a placebo, average *RR* 0.53, 95% CI [0.38, 0.74], 6 RCTs, 4,203 women (Westhoff et al., 2013). Administration of oxytocin before the delivery of the placenta or after did not significantly alter the incidence of PPH, *RR* 0.81, 95% CI [0.62, 1.04], 3 RCTs, 1,167 women (Soltani et al., 2010).

Ergot alkaloids versus placebo. Compared with no uterotonics, oral or intravenous ergot alkaloids significantly reduced the incidence of PPH, *RR* 0.49, 95% CI [0.26, 0.90], 4 RCTs, 3,698 women (Liabsuetrakul et al., 2007).

Tranexamic acid versus placebo. Tranexamic acids significantly reduced the incidence of PPH compared with placebo or no treatment, *RR* 0.44, 95% CI [0.31, 0.64], 3 RCTs, 361 women (Faraoni et al., 2014); *RR* 0.52, 95% CI [0.31, 0.87], 3 RCTs, 1,273 women (Heesen et al., 2014); *RR* 0.52, 95% CI [0.42, 0.63], 6 RCTs, 1,398 women (Novikova et al., 2015).

Early versus late cord clamping. There was no significant difference between the groups for early cord clamping compared to late clamping, *RR* 1.17, 95% CI [0.94, 1.44], 2 RCTs, 2,260 women (McDonald et al., 2013).

Uterine massage versus no uterine massage. There was no significant difference between the groups implementing uterine massage before placental delivery and no massage, *RR* 1.56, 95% CI [0.44, 5.49], 2 RCTs, 1,291 women (Hofmeyr, Abdel-Aleem, et al., 2013). There was no significant difference between the groups implementing uterine massage after placental delivery and no massage, *RR* 0.52, 95% CI [0.16, 1.67], 1 RCT, 200 women (Hofmeyr, Abdel-Aleem, et al., 2013).

Prophylactic management during postpartum period. There was no significant difference between the groups oral methylergometrine after the third stage of labor with placebo, *RR* 1.45, 95% CI [0.39, 5.47], 2 RCTs, 1,097 women (Yaju et al., 2013)

Effect of interventions using therapeutic uterotonics. A total of 18 reviews were identified: four studies about active management of the third stage of labor (Begley et al., 2015; Du et al., 2014; Hofmeyr et al., 2015; McCormick et al., 2002),

seven studies about the use of oxytocin (Jin et al., 2016; McDonald et al., 2004; Mori et al., 2012; Peters, & Duvekot, 2009; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013), four studies about the use of prostaglandins (Joy et al., 2003; Langenbach, 2006; Olefile et al., 2013; Tunçalp et al., 2012), one study about ergot alkaloids (Liabsuetrakul et al., 2007), one study about timing of clamping umbilical cord (McDonald et al., 2013) and one study about uterine massage (Hofmeyr, Abdel-Aleem, et al., 2013). The next section describes only interventions that compared the intervention with placebo or contrasting management.

Active management versus contrasting management. Compared with physiological or expectant management, active management showed significantly more reduction in blood loss when using therapeutic uterotonics, *RR* 0.21, 95% CI [0.17, 0.27], 3 RCTs, 4,855 women (McCormick et al., 2002); average *RR* 0.19, 95% CI [0.15, 0.23], 4 RCTs, 4,829 women (Begley et al., 2015). For the comparison of active management in the third stage of labor with controlled cord traction versus without controlled cord traction, there was no significant difference between the groups, *RR* 0.94, 95% CI [0.88, 1.01], 4 RCTs, 28,229 women (Du et al., 2014); *RR* 0.95, 95% CI [0.88, 1.02], 3 RCTs, 27,829 women (Hofmeyr et al., 2015).

Oxytocin versus placebo. Prophylactic use of oxytocin showed a significant reduction in using therapeutic uterotonics compared with placebo, average *RR* 0.56, 95% CI [0.36, 0.87], 4 RCTs, 3,174 women (Westhoff et al., 2013). Administration of oxytocin before the delivery of the placenta or after does not significantly alter the incidence of using therapeutic uterotonics, *RR* 1.10, 95% CI [0.80, 1.52], 3 RCTs, 1,167 women (Soltani et al., 2010). There was no significant difference between the groups for umbilical vein injection of oxytocin and placebo, *RR* 0.00, 95% CI [0.00, 0.05], 1 RCT, 500 women (Mori et al., 2012).

Ergot alkaloids versus placebo. Compared with no uterotonics, oral or intravenous ergot alkaloids significantly reduced using therapeutic uterotonics, *RR* 0.37, 95% CI [0.15, 0.90], 3 RCTs, 2,698 women (Liabsuetrakul et al., 2007).

Early versus late cord clamping. There was no significant difference between the groups for early cord clamping compared with late clamping, *RR* 1.02, 95% CI [0.44, 2.37], 2 RCTs, 1,345 women (McDonald et al., 2013).

Uterine massage versus no uterine massage. There was no significant difference between the groups implementing uterine massage before placental delivery and no massage, *RR* 1.02, 95% CI [0.56, 1.85], 2 RCTs, 1,260 women (Hofmeyr, Abdel-Aleem, et al., 2013). Implementing uterine massage after placental delivery showed a significant reduction in using therapeutic uterotonics compared with no massage, *RR* 0.20, 95% CI [0.08, 0.50], 1 RCT, 200 women (Hofmeyr, Abdel-Aleem, et al., 2013).

Effect of interventions for mean total blood loss. A total of 16 reviews examining mean total blood loss were identified; three studies about active management of the third stage of labor (Begley et al., 2015; Du et al., 2014; Hofmeyr et al., 2015), six studies about use of oxytocin (Jin et al., 2016; Mori et al., 2012; Peters, & Duvekot, 2009; Soltani et al., 2010; Su et al., 2012; Westhoff et al., 2013), one study about use of prostaglandins (Tunçalp et al., 2012), one study about ergot alkaloids (Liabsuetrakul et al., 2007), three studies about use of tranexamic acid (Ferrer et al., 2009; Heesen et al., 2014; Novikova et al., 2015), one study about the timing of umbilical cord clamping (McDonald et al., 2013) and one study about uterine massage (Hofmeyr, Abdel-Aleem, et al., 2013). Only interventions that compared the intervention with placebo or contrasting management are described next.

Active management versus contrasting management. Compared with physiological or expectant management, active management showed a significant reduction in mean total blood loss, average mean difference (MD) - 78.8 ml, 95% CI [-95.96, - 61.64], 2 RCTs, 2,941 women (Begley et al., 2015). For the comparison of active management in the third stage of labor with controlled cord traction versus without controlled cord traction, controlled cord traction showed significantly reduction mean total blood loss, MD - 10.0 ml, 95% CI [-10.34, - 9.66], 3 RCTs, 4,612 women

(Du et al., 2014); average MD - 10.85 ml, 95% CI [-16.73, - 4.98], 2 RCTs, 27,255 women (Hofmeyr et al., 2015).

Oxytocin versus placebo. Prophylactic use of oxytocin showed a significant reduction in mean total blood loss compared with placebo, MD - 99.46 ml; 95% CI [-181.97, -16.95], 5 RCTs, 1,402 women (Westhoff et al., 2013). Administration of oxytocin before the delivery of the placenta or after did not significantly alter the mean total blood loss, MD 22.32 ml; 95% CI [- 58.21, 102.86], 2 RCTs, 181 women (Soltani et al., 2010). There was no significant difference between the group's umbilical vein injection of oxytocin and placebo, MD -42.48 ml, 95% CI [-49.27, -35.69], 1 RCT, 500 women (Mori et al., 2012).

Ergot alkaloids versus placebo. Compared with no uterotonics, oral or intravenous ergot alkaloids significantly reduced mean total blood loss, MD -81.72 ml, 95% CI [-97.81, -65.63], 3 RCTs, 2,718 women (Liabsuetrakul et al., 2007).

Tranexamic acid versus placebo. Tranexamic acids significantly reduced the incidence of PPH compared with placebo or no treatment, MD -92.37 ml, 95% CI [-108.64, -76.11], 3 RCTs, 461 women (Faraoni et al., 2014); MD -140.29 ml, 95% CI [-189.64, -90.93], 7 RCTs, 1,760 women (Heesen et al., 2014); MD -77.79 ml, 95% CI [-97.95, -57.64], 5 RCTs, 1,186 women (Novikova et al., 2015).

Early versus late cord clamping. There was no significant difference between the groups early cord clamping compared with late clamping, MD 5.11 ml, 95% CI [-23.18, -33.39], 2 RCTs, 1,345 women (McDonald et al., 2013).

Discussion

Overall Completeness and Applicability of Evidence

This systematic review systematically summarised 28 systematic reviews of 7 different methods that included pharmacological and non-pharmacological managements however there were several limitations. This review only focused on interventions that compared placebo or contrasting management. In order to apply to practice, broad-based pharmacological interventions compared to other pharmacological

interventions should be included in our main analysis. Maternal mortality was reported in a few reviews. Because PPH is one of the leading causes of maternal death, more reviews about several interventions would be needed in order to apply in clinical settings. Other outcomes included a large number of data from many trials, but most of the reviews had serious flaws because of high heterogeneity or there were few events about outcomes. This review did not analyse by sub-group. The participants in the reviews experienced a vaginal delivery or caesarean section yet none of the reviews included the risk to participants or the labor interventions. In this systematic review, the researcher did not show the details about participants, settings and interventions. It is difficult to interpret only the evidence from this review to clinical settings.

Quality of The Evidence

The researcher assessed the quality of each systematic review by using the AMSTAR tool (Shea et al., 2007). As a result, the quality of the Cochrane systematic reviews was high; however non-Cochrane systematic reviews varied from low to high. Most of the systematic reviews, in which the quality of the evidence was low, needed to include a comprehensive research analysis and should have provided details about publication bias.

Potential Biases in The Systematic Review Process

This systematic review has several limitations. This systematic review adopted the method in the Cochrane systematic reviews of intervention, which minimized introducing bias at all stages in the review process. This study did a comprehensive search to identify the relevant reviews, however, the author did not use the duplicate process for study selection and data extraction. The author followed a rigorous review process aiming to minimize bias at all stages.

Agreements and Disagreements with Other Studies or Reviews

The WHO published the guideline about prevention and treatment of postpartum haemorrhage (WHO, 2012). In this guideline, many systematic reviews and randomized controlled trials were assessed, which were included in this systematic review. The intrapartum guideline, which is published by the NICE assessed active management of the third stage of labor (NICE, 2014). Several RCTs were included in

the NICE guideline despite the omission of a Cochrane systematic review. However in this systematic review, we were able to include a broader spectrum of published systematic reviews.

Conclusions

Implications for Practice

There were no effective prophylactic managements for maternal mortality. Most methods of effective prophylactic management for PPH were supported by evidence, however they were limited to low or moderate quality of evidence. A higher quality of studies is needed. The participants of reviews had experienced a vaginal delivery or caesarean section and it was unclear about their risks and labor interventions. Therefore, when these prophylactic managements are used, the state of participants and access to medicine should be considered.

Implications for Research

The critical outcome measures about prevention and treatment of PPH are proposed in the guideline of the WHO (WHO, 2012). However, the systematic reviews had a variety of outcome measures as did the individual trials making it difficult to compare results. For example, the outcome about the proportion of PPH had several cut off points, such as greater than or equal to 300, 400 and 500 ml; therefore, it made it difficult to pool results and show all the evidence from similar trials. It is recommended that the trials about preventive interventions for PPH use consistent outcome measures and ones that are recommended in the WHO guideline (WHO, 2012).

Study 2. Uterine Activity during the Two Hours after Placental Delivery among Low-Risk Pregnancies: An Observational Study (Masuzawa & Kataoka, 2016)

Introduction

After the birth of the neonate and placenta, two hemostasis processes are initiated. The primary physiology of postpartum hemostasis involves uterine muscular contractions induced by endogenous oxytocin and prostaglandins. The structure of uterine smooth muscle is spiral in shape and extends in all directions. When the uterine muscles contract, the spiral vessels of the uterus are compressed, and blood flow decreases (Khan & El-Rafaeey, 2012). No studies have reported details of uterine activity during the first two hours after the delivery of the placenta among low-risk women with non-pharmacological intervention during the labor and postpartum. Describing the uterine activity during this critical period, while women in labor are at risk for life-threatening events as PPH, may help to understand the mechanism for uterine atony, and aid in identifying factors related to postpartum hemorrhage brought on by uterine atony.

The purpose of this study was to describe uterine activity within the first two hours after placental delivery among low-risk pregnant women who have undergone no medical treatment during the first to third stages of labor and to explore the relationship between uterine activity and blood loss or pain.

Methods

Study Design, Setting, and Population

This observational study was conducted at two midwifery birth centers located in Japanese metropolitan areas. Participants were experiencing a healthy uncomplicated pregnancy, and subsequently had a low-risk singleton birth at term between December 9, 2014 and May 23, 2015. Both of the midwifery birth centers performed physiological management at the third stage of labor (no routine administration of oxytocin, late cord clamping, and spontaneous delivery of placenta), and skin-to-skin contact immediately after birth.

A total of 33 women eligible for this study were informed verbally and in writing

of their rights as research participants including confidentiality of information and freedom to withdraw without penalty at any time. They all provided written informed consent. Of these, 16 women were excluded with reasons. St. Luke's International University's Institutional Review Board approved this research (14-087).

Data Collection

Uterine activity. Contractile waves of uterine activity were measured by using an external tocodynamometer (Fetal Actocardiograph MT-325, MT-516, TOITU CO., LTD., Tokyo, Japan) as a non-invasive method. During second stage of labor, midwives placed transducers on the women's abdomen to detect uterine contractions and the fetal heart rate. After the delivery, the transducer for fetal heart rate was removed. Then, a clinician assessed the fundus of the uterus through abdominal palpation, followed by the placement of a transducer for uterine contraction below the umbilicus fixed with a belt. After the placental delivery, a clinician re-assessed the fundus of the uterus and placed a transducer on the lower abdomen for the first two hours. During early postpartum, maternal position was supine. However, participants were allowed to change their position if requested.

The data pertaining to uterine contractions and their interval, intensity, and duration, were obtained from the fetal cardiotocography. The rate of paper feed was three centimeters per minute. Definition of contraction interval was time length (minutes) from the first contraction's peak to the second one, and contraction duration was the duration (seconds) at the point of one-fifth intensity from baseline. Two midwives (the author, and a midwife with 13 years of experience) provided interpretations independently. We resolved discrepancies through discussion.

Other variables. Lost blood, just after delivery of the placenta, was collected in a basin placed under the maternal buttocks and with sanitary pads every 30 minutes during the first two hours after placental delivery. The blood in the basin and sanitary pads were weighted on a digital scale. The blood loss with sanitary pads was measured by the weight of pads after subtracting the dry pad weight of 20 grams. Pain levels were measured by using a vertical 100-mm visual analogue scale at every 30-minute intervals during the first two hours after placental delivery. Participants marked their pain level

on the 100-mm line indicating pain from none (0) to the most (100). Demographics and obstetrical characteristics were collected from participants' medical records.

Statistical analysis. The mean contraction parameters were calculated by dividing the data strips into 10 sections, during the last 15 minutes of the second stage of labor, during the third stage of labor and every 15 minutes during the first two hours after placental delivery. The data were calculated for the mean contraction's interval, intensity, and duration of each section. The mean values of each section were compared.

Repeated-measures ANOVA was used for uterine contraction parameters. Spearman's rank-order correlation coefficient was used to analyze between uterine contraction parameters and blood loss or pain ratings. A two-tailed $p < .05$ was considered statistically significant. The statistical analysis was performed using SPSS software (version 22.0).

Results

Data for 17 women were available for analysis. No participants were given labor augmentation with oxytocin, epidural analgesia, or prophylactic administration of oxytocin in the third stage of labor. No women complained of discomfort about continuously putting a transducer on the lower abdomen during the observation period. The demographics and obstetrical characteristics of the participants are presented in Table 3.

Table 3

Demographic and Obstetrical Characteristics

Characteristics	Total (<i>N</i> = 17)
Maternal age, mean (<i>SD</i>), years	32.1 (5.2)
Parity	
Primiparas, numbers	3
Multiparas, numbers	14
BMI, mean (<i>SD</i>), (Kg/m ²)	19.1 (1.7)
Gestational age, mean (<i>SD</i>), week	39.4 (1.0)
Length of labor, median (range), hr	5.4 (1.9, 17.2)
Length of 2 nd stage of labor, median (range), min	36 (6, 107)
Length of 3 rd stage of labor, median (range), min	13 (8, 29)
Laceration	
Intact, numbers	9
1 st degree, numbers	6
2 nd degree, numbers	2
Blood loss, median (range), g	219 (130, 730)
Birth weight, mean (<i>SD</i>), g	3079.2 (308.1)

Patterns of Uterine Activity During Two Hours After Birth

Women were categorized into one of four groups based on factors that may have potentially affected the pattern of uterine contractions including, 1) spontaneous progress, 2) breastfeeding, 3) cooling the uterus, or 4) oxytocin administration.

Spontaneous progress. Seven women were analyzed. Of these, only one was a primipara. The median blood loss was 219 g (range: 130 to 510), and only one woman had PPH (blood loss exceeded 500 g).

Spontaneous uterine activity even during the first two hours after the birth of the placenta exhibited a noticeable pattern of contractions. Contraction frequency decreased with progression over the different stages, $F(9, 54) = 19.7, p < .001$. The mean contraction intervals were 1.9 ± 0.3 min (second stage), 2.4 ± 0.9 min (third stage), and 4.2 ± 0.7 min for the first hour, and 7.9 ± 2.1 min for the second hour after placental birth. Intensity of contractions did not show a marked change across the stages, $F(3.45, 20.75) = 2.63, p = .07$. The mean intensities were 59.0 ± 22.2 mmHg

(second stage), dropping to 33.6 ± 6.4 mmHg, 56.1 ± 13.3 mmHg (third stage), and rising again to 50.8 ± 18.5 mmHg for the first hour and second hour after placental birth. Duration of contractions gradually became longer, $F(3.59, 21.55) = 6.75, p = .001$.

Figure 2 displays an example of spontaneous uterine activity.

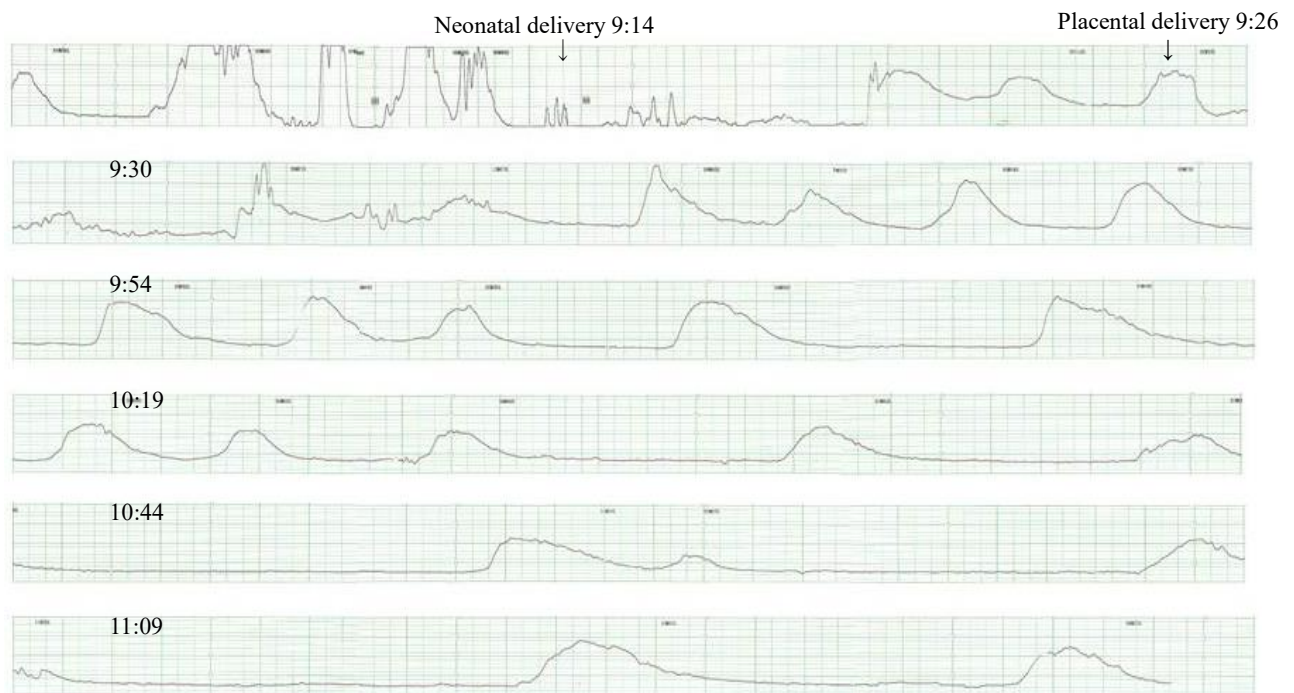


Figure 2. This 37-year-old multiparous woman exhibited good uterine contraction. The measured total blood loss was 261 g. The period within the first two hours after the delivery of the placenta showed a uterine contraction frequency that slightly decreased over time.

Breastfeeding. Six women were analyzed (two primiparas, four multiparous). Their median blood loss was 182.5 g (range: 150 to 305). The timing and duration of suckling by the infants was varied. The mean contraction frequency before breastfeeding was calculated during the last 15 min before the start of suckling; contraction frequency after breastfeeding was calculated during the first 15 min following the end of suckling. Contraction interval with breastfeeding appeared to be shorter than without breastfeeding, but there was no statistical significance, $F(1.15, 4.6) = 2.18, p = .20$. There were no differences in intensity or duration of contractions with or without breastfeeding. Figure 3 shows an example of uterine activity in a woman who breastfed.



Figure 3. Time of the placental delivery was 8:39. This 33-year-old primiparous woman had good uterine contractions and her measured total blood loss was 201 g. She had skin-to-skin contact with her baby during the first hours after birth. Around 30 min after the delivery of placenta, breastfeeding was initiated. During breastfeeding, her contraction intervals become frequent.

Cooling the uterus. The method of cooling the uterus comprised of putting an icepack (270×170×27mm, 1,100g of nonfreezing gel in a plastic bag) wrapped with a cloth on the women's abdomen to cool the uterine smooth muscle through the abdominal wall during two hours after the delivery of the placenta. Two multiparas were evaluated; one had blood loss of 537 and the other 689 g just after delivery but neither had continuous bleeding. There was no difference in contractile waves of uterine activity between using cooling of the uterus and spontaneous uterine contractions. Contraction frequency was slightly decreased, and intensity and duration of contractions showed no change. Figure 4 displays an example of uterine activity in a woman who had uterus cooling.

Neonatal delivery 10:19



Figure 4. This 34-year-old multiparous woman did not have good uterine contractions but no continual bleeding. Her measured total blood loss was 537 g.

Administration of oxytocin. Two multiparas had continuous bleeding just after the delivery of the placenta, and each had a boggy uterus through abdominal palpation. One women lost 483 g and the other 730 g of blood. Thus, they were treated with intravenous infusion of oxytocin (5 IU in 500 ml, 150 ml per hr). Uterine contractions were frequent, induced by oxytocin, and the mean contraction interval was 3.5 ± 2.0 min. Figure 5 displays an example of uterine activity in a woman who treated with intravenous infusion of oxytocin.

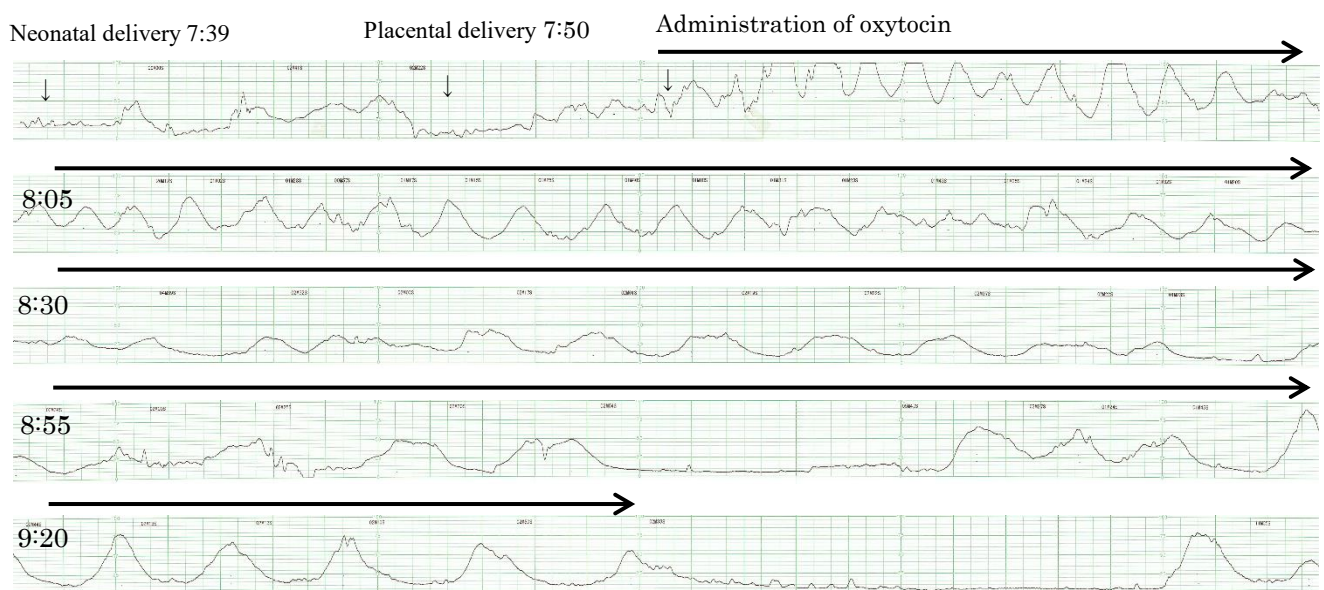


Figure 5. This 25-year-old multiparous woman had boggy uterus and continues bleeding. The amount of the blood loss just after placental delivery was 390 g. Her measured total blood loss was 483 g.

Correlation of uterine activity with blood loss, or with pain. No correlation was found between blood loss and contraction frequency ($\rho = .21, p = .40$), intensity ($\rho = -.05, p = .84$), duration of contractions ($\rho = .07, p = .76$). Likewise, no correlation was found between the mean pain ratings and contraction frequency ($\rho = .39, p = .11$), intensity ($\rho = .24, p = .34$), duration of contractions ($\rho = .08, p = .75$).

Discussion

To our knowledge, this study is the first to characterize spontaneous uterine activity in low-risk pregnant women who have not undergone pharmacological intervention. Comparing the postpartum uterine contraction patterns of previous studies (Hendricks, Eskes, & Saameli, 1962; Hendricks, 1968), the uterine contraction intervals were shorter with oxytocin, the tendency to decrease in frequency over time among low-risk pregnant women without intervention during the labor stages was similar to women who had oxytocin and epidural analgesia. The uterine contraction intervals become prolonged over time, and blood loss did not increase. In this study, no correlation was found between blood loss and uterine activity parameters. This result is in line with those of previous studies (Hendricks, 1968; Chua et al., 1996). It is important to acknowledge that the mechanism involved in hemostasis includes not only contraction of the myometrium, but also coagulation factors. Although this finding could apply to low-risk women without PPH, further studies need to be undertaken that include consideration of coagulation factors.

Contraction frequency during breastfeeding was increased, and contraction intervals with breastfeeding were shorter than without breastfeeding. Similarly, previous studies (Hendricks, 1968; Chua et al., 1996) noted the effectiveness of breastfeeding for postpartum uterine activity in women with administration of prophylactic oxytocin and reported increasing uterine activity with breastfeeding.

Cooling the uterus is one of the unique non-pharmacological prophylactic management strategies for PPH in Japan. Cold therapy and the somato-visceral reflex decreases the blood flow of the uterus; thus, cooling the uterus could prevent PPH. However, the results of this study do not provide support for an effect of cooling the

uterus on the contraction of the myometrium. The previous study (Osumi & Horiuchi, 2007) was observational in design, and therefore, confounding factors may have affected the results. Furthermore, the number of subjects was very small. Further studies focused on examining the role of cooling the uterus on blood flow with larger sample size and improved research design is necessary.

Uterine contraction frequency measured by external tocodynamometry has been shown to have good correlation with intrauterine pressure catheters (Paul & Smeltzer, 1991). However, the external tocodynamometer does not detect intensity of contractions with precision when compared with intrauterine pressure catheters (Paul & Smeltzer, 1991).

While we believe, our findings provide insight into improved understanding of the relationships between myometrium contractions and blood loss and between pain, further research should be undertaken in a larger sample size to include the consideration of coagulation factors and improved methods for uterine activity measurement.

Conclusion

Author's Conclusion

This study aimed to characterize uterine activity during the two hours after the placental birth among low-risk pregnant women by using an external tocodynamometer, and then to determine the relationship between uterine activity and blood loss or pain. Spontaneous uterine contraction frequency after the birth slightly decreased over time, however, blood loss did not increase. Uterine contractions were frequent when induced by oxytocin administration and infant's suckling; however, cooling the uterus did not change the contraction waves. Additional research in a larger population could help to confirm these results and further improve our understanding of spontaneous uterine activity during early postpartum.

Implication for Research

There were no correlations between the variables, the number of uterine contractions and the amount of blood loss. Thus, the number of the uterine contractions

is not necessary to include in research outcomes about postpartum hemorrhage.

Methods

Study Design

This randomized controlled trial compared the intervention group who had cooling the lower abdomen during the first two hours after the placental delivery with the comparison group not cooling the lower abdomen, in order to verify the effect of prevention for PPH.

Participants

This randomized controlled trial was conducted in a perinatal medical center in Tokyo, Japan. The eligibility requirements of this study were women expecting to deliver vaginally at the hospital, and to have a singleton pregnancy with cephalic presentation at or more than 34-week gestation. This study excluded women with placenta previa, previous severe PPH, intrauterine fetal death, multiparity (four or more), pre-eclampsia, polyhydramnios, estimated fetal birth weight over 4,000 g, pre-pregnancy BMI over 40, blood coagulation disorder, taking any anticoagulants, pregnancy-induced hypertension, hepatic dysfunction, placental abruption, caesarean section birth, induction and augmentation of labor with oxytocin, administration of prophylactic oxytocin during the third stage of labor and those who did not understand Japanese.

Randomization and Masking

Participants were randomly assigned to a cooling the lower abdomen group or no intervention group at the time of placenta delivery, by use of a web-based computer site, with permuted blocks of six and stratified by parity. When the participants delivered the placenta, the investigator accessed the website and checked the allocation. After the decision of the allocation group, the researcher told the caregiver about the allocation.

Participants and caregivers could not be masked, because of the nature of this intervention. The data were not masked to allocation when investigator analyzed.

Procedures

Before starting recruitment for this study, the midwives and obstetricians were trained and received an explanation with a document (see Appendix1) about how to cool

the lower abdomen. Early cord clamping and controlled cord traction were applied as the management of the third stage of labor, the room temperature was 80.6 °F in both groups.

The intervention method was putting 47.3 °F icepack (ICE-NON[®]; Hakugen Earth CO., LTD., Tokyo, Japan, 270×170×27mm, 1,100 g of nonfreezing gel in a plastic bag) covered with a towel on the lower abdomen for two hours, using the pubic bone as the basic point. This cooling method is implemented in Japanese clinical settings. After the randomization, midwives assessed the position and hardness of the fundus of the uterus through abdominal palpation, and put the icepack on the women's lower abdomen. This icepack was cooled in a freezer for more than eight hours, in order to keep the same surface temperature of the icepack during intervention. If women in the intervention group felt discomfort about putting an icepack on her lower abdomen, midwives removed the icepack and cooling was stopped. In the previous intervention study about cooling the lower abdomen of women in childbirth with the icepack, surface temperature was 47.3 °F, for four hours after expulsion of the placenta (Hayashi et al., 1995), the skin surface temperature of the participants' lower abdomen was measured by a thermometer (Coretemp[®] CM-210; TERUMO Corporation, Tokyo, Japan) three times: just after placental delivery (before starting the intervention), two hours and four hours after the placental delivery. In the cooling group, the mean skin surface temperatures were 91.76 °F (at placental delivery), 77.9 °F at two hours, and 73.0 °F at four hours after placental birth. In the non-cooling group, the mean skin surface temperatures were 90.5 °F (at placental delivery), 90.5 °F at two hours, and 91.2 °F at four hours after placental birth. In the other observational study about cooling the lower abdomen of women in childbirth (Osumi & Horiuchi, 2007), the researcher measured the surface temperature of the participants' lower abdomen using by a thermometer (Coretemp[®] CM-210; TERUMO Corporation, Tokyo, Japan) for 105 minutes (at the beginning and completion of cooling). The mean skin surface temperatures were 73.0 ± 37.7 to 82.7 ± 36.6 °F. Any adverse effect of the cooling the lower abdomen, for example chilblains, had never been reported in previous studies. However, an observational study (Osumi & Horiuchi, 2007), the researchers found that

women described feeling cold and discomfort caused by cooling the lower abdomen; eight people of 16 participants felt the cold and of those, four felt discomfort.

At the planning of this randomized study, the mean skin surface temperatures of lower abdomen of non-pregnant with the icepack, which cooled and covered with a towel in accordance to the protocol of this randomized study, were measured by a thermometer (Coretemp[®] CM-210; TERUMO Corporation, Tokyo, Japan) for 120 minutes. The skin surface temperatures were 92.6 °F (before cooling), 80.0 °F at five minutes, and 70.7 °F at 10 minutes. After that, the mean skin surface temperatures were 67.1 ± 33.4 °F for 120 minutes.

In the control group, women had no intervention, which was not putting the ice pack on the lower abdomen and no cooling. Except for the intervention, the women of the both groups received the same management by midwives and obstetricians.

If the participants had abnormal bleeding, midwives and obstetricians gave treatments priority to this research and the treatments were provided at the discretion of the individual physician in the both groups.

Outcomes

The outcomes were decided in line with the critical and important outcomes for decision making from the guidelines of the WHO about prevention and treatment of PPH (WHO, 2012).

The primary outcome was the amount of total blood loss (grams) within the two hours after the newborn delivery. The secondary outcomes were the incidence of blood loss of 500 g or more and 1,000 g or more, use of therapeutic uterotonics, use of blood transfusion, postpartum anemia, transport to tertiary emergency medical facility, any side effect of intervention, nausea, vomiting, headache, breast feeding, discomfort at cooling, and abdominal pain.

Data Collection

Permission for this study was sought in writing from the representative and director for nursing of the perinatal medical center or orally (Appendix 2). After the implementation of this study was allowed, a poster of information disclosure (Appendix 3) was posted on the bulletin board in the medical center. The researcher selected

eligible participants supported by midwives' by reviewing the medical records. The eligible women were informed about this study by both written information (Appendix 4) and verbally during their prenatal examination of at least 34 weeks' gestation. The women agreed to participate by signing a consent form (Appendix 5). Women were informed that, in case of emergency caesarean section, induction and augmentation of labor with oxytocin, and administration of uterotonics during the third stage of labor, they had to be excluded from this study even though they had agreed to participate. In addition, they were told they could retract their consent without penalty by using the withdrawal document (Appendix 6).

Demographic data. Demographic data (age, height, weight, parity, and history of PPH), and obstetrical characteristics (gestational age, neonatal birth weight, mode of the delivery, presence of perineal laceration, vital signs during the first two hours after the delivery), were collected using a data sheet (Appendix 7) that was filled out by a researcher using participants' medical records.

Pain levels with uterine contraction. Pain levels with uterine contraction were measured by using a vertical 100-mm visual analogue scale at one-hour intervals during the first two hours after placental delivery. Participants marked their pain level on the 100-mm line indicating pain from none (0) to the most (100) (Appendix 8, 9, 10, 11, 12, 13).

Ice-pack discomfort levels. Feelings of discomfort from the ice pack were measured by using a vertical 100-mm visual analogue scale at one-hour intervals during the first two hours after placental delivery. Participants marked their discomfort level on the 100-mm line indicating discomfort from none (0) to the most (100) (Appendix 11, 12, 13).

Blood loss within two hours after delivery. Just after newborn delivery, the midwives removed the mat soaked with amniotic fluid and placed a new mat under the women's buttocks. This new mat was placed until placental delivery, and blood in the mat was weighted as blood loss at the third stage of labor. The midwife replaced the mat with a sanitary pad immediately after the expulsion of the placenta. Lost blood was collected with sanitary pads the first and second hour after placental delivery. The blood loss with

mat and sanitary pads were weighted on a digital scale, and measured by the weight of mat and pads after subtracting the dry mat weight of 270 grams and the dry pad weight of 20 grams.

Other variables. Other variables were collected from participants' medical record; strength of uterine contractions, treatment for PPH and adverse effect from the treatment, adverse effect of the cooling, blood test data about anemia (hemoglobin, hematocrit, Fe, MCV and MCH) before and after the delivery, absence of treatment for anemia, and breastfeeding during hospitalization.

The researcher monitored the adherence to protocol about putting the mat, the duration of the ice pack, and the method of cooling.

Instead of the participants' name an identification number was written on the data sheet (Appendix 7) and questionnaire (Appendix 8, 9, 10, 11, 12, 13), thus the personal information was protected. The codebook for the corresponding values between participants' name and the identification number was prepared, and kept in a lock-fast drawer.

Statistical Analysis

The primary outcome was the amount of total blood loss (grams) within the two hours after the newborn delivery. The sample size was calculated on data from a previous study (Sato et al., 1984). This study had 80% power at the 5% significance level to detect the mean difference of the total blood loss of 70 grams between the two groups. Thus, the sample size was calculated as 144 women (72 women per group).

The primary analysis was by intention to treat for comparing two groups. The secondary analysis was by per-protocol. For comparison between the two groups, the t-test was used for continuous variables and mean difference was calculated. The chi-square test for dichotomous variables was applied and relative risk with 95% CI was calculated.

The mean blood loss during the third stage of labor, which was a baseline characteristic, was not well balanced between the groups. Therefore, an analysis of covariance (ANCOVA) with the covariate for the amount of blood loss during the third stage-labor, which was not a pre-specified analysis, was performed to describe the effect

of cooling the lower abdomen for reducing the amount of postpartum blood loss during cooling.

The statistical analysis was performed using SPSS software (version 24.0).

Ethical Considerations

The “Ethical Guidelines for Medical and Health Research Involving Human Subjects” guided the study protocol:

- Whether to participate or participate in this research was to be based on the will of the research participants. Before publication, it was possible to withdraw the consent of research participation.
- If women did not participate, or withdrew their consent of research participation during the study, they did not suffer any disadvantage. If women withdrew their consent, the research data collected up to that point would be discarded if the women desired to discard data.
- Even if women participated in the research, as usual, women were able to receive maternal care for two hours after parturition from obstetricians and midwives at the research cooperation facility. Participation in the research would not interfere with breast-feeding.
- Those participating in the research may not experience any benefits by participating however the results of this study will be utilized to establish preventive management for postpartum hemorrhage. The disadvantage of participating with this research is, that it required participant’s effort to answer the questionnaire. Also, in the case of the intervention group, there was a possibility of discomfort due to cooling the lower abdomen during the two hours after the delivery.
- If women wanted to stop cooling the lower abdomen, they could stop. As usual, the midwives of the research cooperation facility observed whether physical influences such as frostbite had occurred while cooling the lower abdomen. There had been no reported cases of physical influences caused by cooling the lower abdomen after parturition. In the unlikely event of a physical influence such as frostbite, there will be consultation with a physician at the research cooperation facility so that appropriate treatment could be received. In the event that a physical condition

occurred due to the intervention of this research, the treatment provided would be compensated by the insurance covered by the researcher, but not compensated by money to the participant.

- The data sheet does not identify the participant's name and performs encoding. Anonymity of research participants and protect personal information and privacy is always ensured. After obtaining consent to participate in the research, the researcher adds the name to the prepared correspondence table of ID number and name. This correspondence table was stored in a place where a key is placed very separate from the data.
- The data sheets were stored in the locked place and strictly managed so that only the researcher could use it. The collected data was protected so that anonymity was maintained and stored in a password protected personal computer and flash memory. In addition, password management was thorough so that only the researcher could access it.
- Information that anonymized personal information was not used for purposes other than this research. Also, it shall be kept for five years from the date of reporting the end of this research, or three years after publication to academic journals or academic societies, whichever is longer, but other information was destroyed after the study was over.
- This research will be presented as part of a doctoral dissertation.
- The researcher's Institutional Review Board approved the research (No. 15-062).
- The research cooperation facility's Institutional Review Board approved the research (Katsushika Maternity Red Cross Hospital, No. 1505)
- This trial was registered with UMIN-CTR (ID: UMIN000019834).
- This study was insured by; Will and e-kango which is the comprehensive compensation system of the Japan Nursing School Council Co-organizing Society.
- JSPS KAKENHI Grant Number 26670993 supported this study. The YAMAJI FUMIKO NURSING RESEARCH FUND, and Grant-in-Aid for Epidemiological Research, St. Luke's International University.

Results

The researcher deemed 262 women to eligible, of whom 231 consented to participate between January 2016 and May 2016. When the sample size was reached, the recruitment was stopped. After the start of labor, 71 women were excluded with the following reasons: 47 received labor augmentation, 22 gave childbirth by emergency caesarian section, one had an oxytocin injection during the third stage of labor, and one accidentally delivered at home. Thus, a total of 160 women were randomly assigned to cooling the lower abdomen ($n = 81$) or to no intervention ($n = 79$). The flow of recruitment and participants are shown in Figure 6. No women were lost to follow up in the current study.

Baseline characteristics were similar in both groups except for the mean blood loss during the third stage of labor (Table 4).

Almost all the participants received allocated management; 80 (98.8%) of 81 women received cooling the lower abdomen in the intervention group and 77 (97.5%) of 79 women in the control group. As Table 5 indicates, 139 (86.9%) were placed on a new blood collector mat before placental delivery. No adverse events occurred but, seven (8.7%) women in the intervention group decline to continue cooling the lower abdomen because of discomfort. Except for the intervention, other prophylactic managements for PPH such as uterine massage or nipple stimulation were not performed in either group.

Trial outcomes are shown in Table 6. As the primary outcome, mean total blood loss within the two hours after the placental delivery was not reduced in the cooling group compared to the control group (513.3 g versus 478.1 g, MD 35.2 g, 95% CI [-65.3, 135.7]).

Intention-to-treat analysis showed, the incidence of blood loss of 500 g or more during the two hours after the delivery was not decreased in the cooling group compared to no intervention group (44.4% versus 35.4%, *RR* 1.21, 95% CI [0.86, 1.7]). There was not a significant difference in the incidence of blood loss of 1,000 g or more between the two groups (7.4% versus 7.6%, *RR* 0.98, 95% CI [0.55, 1.78]). The use of therapeutic uterotonics was higher in the control group, but there was no significant difference (39.5% versus 50.6%, *RR* 0.79, 95% CI [0.58, 1.09]). There were no

participants in either group who required blood transfusion. The mean total blood loss (*SD*) within two hours did not differ between the two groups in per-protocol analysis: 508.3 (314.8) g ($n = 73$) in the intervention group and 482.0 (311.4) g ($n = 77$) in the control group, respectively. There was no significant difference between the two groups regarding: the incidence of blood loss of 500 g or more (45.2% (33/73 women) versus 35.1% (27/77 women), *RR* 1.18, 95% CI [0.90, 1.54]); the incidence of the blood loss of 1,000 g or more (6.8% (5/73 women) versus 7.8% (6/77 women), *RR* 0.99, 95% CI [0.90, 1.08]), and the incidence of using therapeutic uterotonics (37.0% (27/73 women) versus 50.6% (39/77 women), *RR* 0.78, 95% CI [0.58, 1.04]).

In the cooling group, seven (8.6%) women reported discomfort with cooling the lower abdomen, and declined to continue cooling. Subjective outcomes about pain with uterine contraction in both groups and discomfort with cooling among intervention group are displayed in Table 7. There were no severe outcomes, such as maternal death and transportation to tertiary medical facilities.

The amount of the blood loss during the first two hours after the placental delivery was not set for outcomes; instead it was the amount of blood loss during the intervention. Mean total blood loss was not reduced in the cooling group compared to the no intervention group (513.3 g versus 478.1 g, MD 35.2 g, 95% CI [-65.3, 135.7]). However, considering only the intervention period, the mean amount of the blood loss during the first two hours after the placental delivery was less in the group of cooling in comparison to no intervention (60.6 g versus 82.0 g, MD -21.5 g, 95% CI [-46.0, 3.0]). The premise was assessed and ANCOVA with the covariate for the amount of blood loss during the third stage-labor was used. ANCOVA showed that cooling the lower abdomen might reduce the total blood loss (mean blood loss with standard error (*SE*) 485.8 (8.7) g versus 506.4 (8.8) g, MD -20.6 g, 95% CI [-45.18, 4.06], $p = .10$), and the blood loss during first two hours after placental delivery (mean blood loss (*SE*) 61.0 (8.7) g versus 81.6 (8.8) g, MD -20.56 g, 95% CI [-45.18, 4.06], $p = .10$).

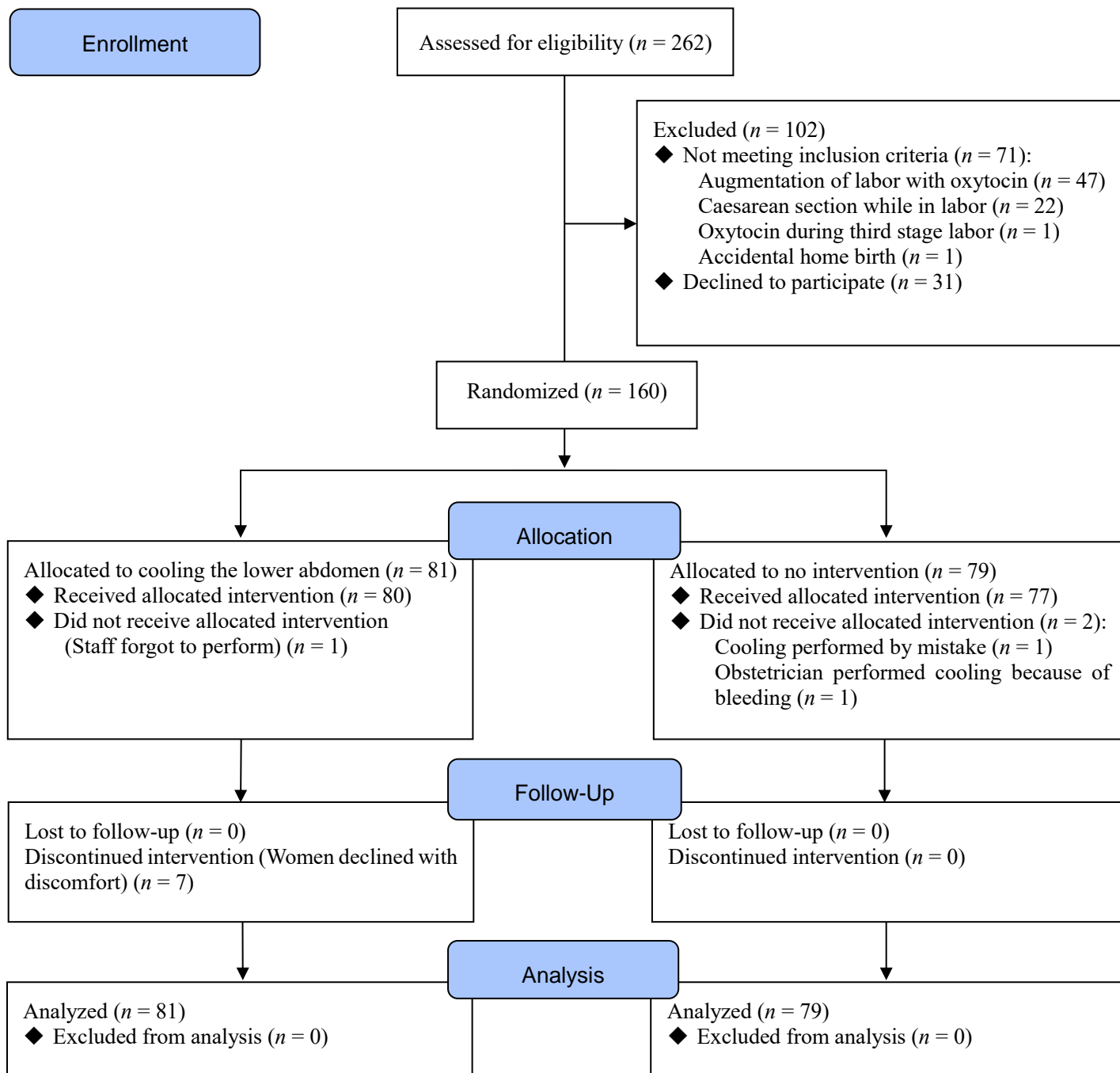


Figure 6. Trial flow diagram.

Table 4
Baseline Characteristics of The Study Participants. Values are numbers (percentages) of women.

Characteristics	Cooling the lower abdomen (<i>n</i> = 81)	No intervention (<i>n</i> = 79)
Maternal age, mean (<i>SD</i>), (years)	32.5 (5.6)	32.4 (5.6)
Parity		
0	36 (44.4)	33 (41.8)
1	29 (35.8)	32 (40.5)
2	14 (17.3)	11 (13.9)
3	2 (2.5)	3 (3.8)
Body mass index, mean (<i>SD</i>), (Kg/m ²)	21.0 (3.4)	20.6 (2.7)
Prenatal hemoglobin, mean (<i>SD</i>), (g/L)	11.5 (0.8)	11.4 (0.8)
Prenatal hematocrit, mean (<i>SD</i>), (%)	34.6 (2.3)	34.6 (2.5)
Gestational age, mean (<i>SD</i>), (weeks)	39.4 (1.2)	39.5 (1.2)
Length of 1 st and 2 nd stage of labor, mean (<i>SD</i>), (hours)	7.0 (4.6)	6.8 (4.9)
Length of 3 rd stage of labor, mean (<i>SD</i>), (minutes)	10.1 (8.3)	9.6 (7.5)
Prelabor rupture of membranes	20 (25.3) (<i>n</i> = 79)	20 (25.3)
Delivery position		
Supine	58 (71.6)	60 (75.9)
Lateral	17 (21.0)	13 (16.5)
Hands and knees	4 (4.9)	5 (6.3)
Squat	0	1 (1.3)
Stand	2 (2.5)	0
Instrumental delivery		
Vacuum extraction	2 (2.5)	3 (3.7)
Forceps delivery	0	1 (1.2)
Episiotomy	12 (14.8)	9 (11.4)
Number of women with lacerations		
Intact	7 (8.6)	5 (6.3)
1 st degree	7 (8.6)	16 (20.3)
2 nd degree	66 (81.5)	56 (70.9)
3 rd degree	1 (1.2)	2 (2.5)
Vaginal hematoma	1 (1.2)	0
Vaginal arterial trauma	1 (1.2)	0
Placenta accreta	0	1 (1.2)
Placental abruption	1 (1.2)	0
Median blood loss at 3 rd stage (range), grams	365.0 (58-1825)	334.0 (50-1584)
Birth weight, mean (<i>SD</i>), grams	3,050.1 (390.3)	3,013.8 (356.1)

Table 5
Adherence to Allocated Intervention and Other Aspects of Management.

Variables	Cooling the lower abdomen (n = 81)	No intervention (n = 79)
Blood collector mat in place before placental delivery	71/ 81 (87.7)	68/79 (86.0)
Receive allocated intervention	80/81 (98.8)	77/79 (97.5)
Putting an icepack according to protocol	73/81 (90.1)	-

Table 6
Trial Outcomes by Intention to Treat Analysis

Outcomes	Cooling the lower abdomen (n = 81)	No intervention (n = 79)	Relative risk [95% CI]	Mean difference [95% CI]	p value
Mean blood loss at 3 rd stage (SD), grams	452.7 (333.5)	396.1 (299.4)	-	56.7 [-42.4, 155.7]	.26
Mean blood loss during the first 2 hours after placental delivery (SD), grams	60.6 (51.6)	82.0 (98.6)	-	-21.5 [-46.0, 3.0]	.086
Mean total blood loss (SD), grams	513.3 (333.2)	478.1 (310.1)	-	35.2 [-65.3, 135.7]	.49
Blood loss ≥500 g	36 (44.4)	28 (35.4)	1.21 [0.86, 1.7]	-	.26
Blood loss ≥1000 g	6 (7.4)	6 (7.6)	0.98 [0.55, 1.78]	-	1.00
Transportation to tertiary medical facilities	0	0	-	-	-
Blood transfusion for postpartum hemorrhage	0	0	-	-	-
Therapeutic uterotonics after placental delivery	32 (39.5)	40 (50.6)	0.79 [0.58, 1.09]	-	.20
Oxytocin (5 IU)	22 (27.2)	19 (24.1)	-	-	-
Oxytocin (10 IU)	7 (8.6)	13 (16.5)	-	-	-
Oxytocin (15 IU)	2 (2.5)	6 (7.6)	-	-	-
Oxytocin (20 IU)	1 (1.2)	2 (2.5)	-	-	-
ergo-metrine	2	3	-	-	-

Mean peripartum change in hemoglobin, mean (<i>SD</i>), (g/L)	1.2 (1.2)	1.0 (1.0) (<i>n</i> = 78)	-	0.16 [-0.20, 0.51]	.30
Mean peripartum change in hematocrit, mean (<i>SD</i>), (%)	2.9 (3.8)	2.5 (3.2) (<i>n</i> = 78)	-	0.44 [-0.66, 1.55]	.42
Breastfeeding	51 (63.0)	44 (55.7)	-	-	-
Breastfeeding with formula	21 (25.9)	31 (39.2)	-	-	-
Any side effect of intervention					
Burning pain	0	0	-	-	-
Blistering of the skin	0	0	-	-	-
Nausea	0	0	-	-	-
Vomiting	0	0	-	-	-
Diarrhea	0	0	-	-	-
Headache	0	0	-	-	-
High blood pressure	0	0	-	-	-

Table 7
Subjective Outcomes about Pain and Discomfort

Variables	Cooling the lower abdomen (<i>n</i> = 81)	No intervention (<i>n</i> = 79)
Mean pain just after placental delivery (<i>SD</i>)	18.7 (24.1) (<i>n</i> = 77)	19.9 (23.9) (<i>n</i> = 75)
Mean pain at 1 hour (<i>SD</i>)	24.7 (24.5) (<i>n</i> = 77)	28.4 (23.9) (<i>n</i> = 75)
Mean pain at 2 hours (<i>SD</i>)	21.0 (23.2) (<i>n</i> = 77)	25.3 (24.8) (<i>n</i> = 75)
Mean discomfort by putting an ice pack just after placental delivery (<i>SD</i>)	10.9 (21.5) (<i>n</i> = 79)	-
Mean discomfort by putting an ice pack at 1 hour (<i>SD</i>)	13.5 (21.5) (<i>n</i> = 79)	-
Mean discomfort by putting an ice pack at 2 hours (<i>SD</i>)	9.4 (17.8) (<i>n</i> = 74)	-

Discussion

In this randomized controlled trial, the principal finding was that cooling the lower abdomen did not reduce the amount of total blood loss in the two hours after delivery compared to no intervention group. The proportion of the women who had PPH was not lower in the cooling group compared to the control group, and there was no significant difference in blood loss of 1,000 g or more between the two groups. To the best of our knowledge, the current study is the first randomized controlled trial to compare cooling the lower abdomen with a control group among the women who had a vaginal delivery with no prophylactic uterotonics in the third stage of labor.

The total amount of blood loss in the two hours after delivery in the cooling group was more than in the no intervention group (513.3 g versus 478.1 g) by t-test, and the cooling the lower abdomen seemed to increase the amount of blood loss. However, a different picture emerges when the results are analyzed using ANCOVA. Using the parameter of the intervention period, which was the blood loss at the first two hours after the placental delivery, the cooling group had less loss than the comparison group (60.6 g versus 82.0 g) by t-test. Furthermore, ANCOVA also showed that cooling the lower abdomen reduced a small amount of the blood loss during the first two hours after the delivery.

Reducing the amount of the total blood loss by cooling the lower abdomen was not demonstrated, but not increasing the blood loss which was shown by t-test. Cooling may reduce the amount of the blood loss during the first two hours after the placental delivery. However, the effect of the reducing the blood loss was very small; in addition, all participants among the intervention group felt discomfort. The degree of discomfort was small, and seven (8.7%) women decline to continue cooling the lower abdomen because of their discomfort. Given the balance of benefits and harms, this study indicates that cooling the lower abdomen for preventing PPH may not be useful for the women who deliver in the medical facilities and who are able to easily access the medical facilities.

In a Japanese non-randomization study (Sato et al., 1984) in which subjects were given a methylergometrine injection in the third stage of labor, in the group

receiving cooling the lower abdomen during two hours after the neonatal delivery ($n = 101$) had significantly less mean total blood loss during two hours after newborn delivery compared to the non-cooling group ($n = 102$) (266.3 g versus 336.5g, $p < .05$). The authors surmised that cooling the lower abdomen affected the uterine contractions, and cooling the lower abdomen along with methylergometrine reduced the blood loss. In contrast, the results of our study did not show the effect of cooling the lower abdomen to reduce the total blood loss. Another randomized controlled trial (Mitchell, Stecher, Crowson, & Rich, 2015) verified that uterine cooling during cesarean section reduced blood loss. They put sterile sponges soaked with sterilized saline of 30 °F on the uterus during the suturing of the uterine incision after the newborn delivery. The mean blood loss during and after the three-hour operation, in the uterine cooling group ($n = 100$) was significantly reduced compared to the non-cooling group ($n = 100$) (536 g versus 756 g), because cooling induced uterine contractions. Cooling the uterus during cesarean delivery was much more effective than cooling the lower abdomen after the delivery. Several studies reported on cooling of rats. Muscular contractions were observed by cooling rats' digestive organs and the bladder which consisted of smooth muscle (Mustafa & Thulesius, 1999, 2001), Yet no study has observed the changes in the uterus muscular structure by cooling of the uterus. However, when the temperature of uterine tissues reaches 68 to 75.2 °F induced by the cooling, potassium ions in the smooth muscle cells are reduced, and muscle contraction is caused by the influx of increased calcium ions from the extracellular fluid (Nasu, 1990). Moreover, cooling has the effect of a somato-visceral reflex (Harmer, 1957). Cooling the uterus through the abdominal wall may not work well enough compared to cooling the uterus directly, and the effect of somato-visceral reflex by putting the cold pack on the lower abdomen may be smaller.

Considering the generalizability, the mean Japanese birth age at the first baby is 30.7-year-old, and at the second baby is 32.5-year-old and, the mean body mass index among Japanese pre-pregnancy women in their 30's is $21.8 \pm 3.7 \text{ kg/m}^2$ (Ministry of health, Labor and Welfare, 2015). The build and age of participants were similar to the average Japanese women of similar ages. Hence, the findings of this study may be

applicable for the women having a spontaneous vaginal delivery with no prophylactic uterotonics during the third stage of labor.

From our findings of cooling the lower abdomen did not provide an additional benefit when not taking prophylactic uterotonics during the third stage of labor, and therefore, it may not be necessary as the preventing management for PPH after vaginal delivery. Implementation of the cooling the lower abdomen was somewhat offensive to women and the procedure takes time and effort to prepare the cold pack for medical staff. Not providing cooling to the lower abdomen will help eliminate the discomfort of women due to cold, and reduce the burden of Japanese midwives and obstetricians. Support for eliminating cooling the lower abdomen is based on the evidence documented by this study.

There are some limitations of the study. Although the design of this study was a randomized controlled trial it was not possible for it to be a blind or double blind study. Therefore, there may have been some bias among clinicians. However, the primary outcome was the amount of blood loss was an objective indicator. So, the reliability was not threatened by non-masking about primary outcome. The proportion of women receiving therapeutic uterotonics in the control group was more than in the cooling group and the median blood loss during the third-stage in the control group was less than in the cooling group. There is a possibility of diagnostic bias because of non-masking of obstetricians. Even though it was a randomized controlled trial, and the amount of blood loss during the third stage of labor was one of the baseline characteristics and affected the amount of total blood loss, the two groups were not equal at baseline. So, in order to increase the precision, it is necessary to provide in the inclusion criteria parameters about the blood loss during the third-stage. The primary outcome of this study was the amount of the total blood loss. Further research is needed that sets the primary outcome as the incidence of blood loss or more than 1,000 ml, which is one of the important outcomes, and with a larger sample size.

Conclusion

Cooling the lower abdomen did not decrease the blood loss compared with no cooling among the women who had vaginal delivery with no prophylactic uterotonics in the third stage of labor. There was no decrease in the number of the women who had PPH and severe PPH in the cooling group compared to the control group. Cooling the lower abdomen is one of the unique non-pharmacological prophylactic managements for PPH in Japan, but women felt discomfort with cooling and no effectiveness was found for reducing blood loss. Cooling the lower abdomen may not be useful for reducing blood loss in the first two hours after delivery for the women who deliver in the medical facilities.

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