博士論文

Does oxytocin administration during the first and second stages of labor increase the risk of postpartum hemorrhage? A case-control study at a National Maternity Hospital in El Salvador

（分娩第 1 期・第 2 期のオキシトシン投与は、産後多出血のリスクを増大させるか？
エルサルバドル国立産科病院における症例対照研究）

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Acronyms and abbreviations

AMTSL	Active management of third stage of labor
BMI	Body mass index
CCT	Controlled cord traction
IU	International units
LBW	Low birth weight
MMR	Maternal mortality ratio
MOH	Ministry of Health
PPH	Postpartum hemorrhage
SPPH	Severe postpartum hemorrhage
UNICEF	United Nations Children's Fund
VIF	Variance inflation factor
WHO	World Health Organization

Abstract

Background

Postpartum hemorrhage (PPH) is a major cause of maternal death. This study aimed to investigate the risk factors for PPH, specifically according to the level of exposure to oxytocin during the first and second stages of labor.

Methods

Using a case-control design, we compared 263 cases of PPH (blood loss ≥ 500 g) and an equivalent number of controls who gave birth at the Salvadoran National Maternity Hospital between April and June 2014. Quantitative data regarding oxytocin administration were categorized as low or high levels of oxytocin exposure.

Results

Labor augmentation was not associated with the risk of PPH (adjusted odds ratio [OR]: 1.50, 95% CI: 0.91–2.46), and there was insufficient evidence to indicate a clear association between the level of oxytocin exposure and the risk of PPH. However, second- to fourth-degree perineal tears (adjusted OR: 5.12, 95% CI: 1.40–19.16), vaginal laceration (adjusted OR: 3.26, 95% CI: 1.22–8.75), and episiotomy (adjusted OR: 1.95, 95% CI: 1.29–2.94) were important risk factors for PPH. In addition, traumatic bleeding was responsible for 76.0% of the PPH cases that we observed.

Conclusions

Labor augmentation was not a risk factor for PPH, and a clear dose-response

relationship with oxytocin use was not observed. In addition, severe perineal tear, vaginal laceration, and episiotomy were associated with an increased risk of PPH (approximately 5-fold, 3-fold, and 2-fold, respectively). However, as genital tract laceration and uterine atony were associated with labor induction and augmentation, oxytocin should be utilized carefully during the first and second stages of labor.

Keywords

Postpartum hemorrhage, Risk factor, Induction of labor, Augmentation of labor, Oxytocin, Episiotomy, Medical interventions, Maternal death, El Salvador

1. Introduction

1.1. Background

1.1.1. Maternal death due to postpartum hemorrhage

More than 300,000 women die each year due to complications of pregnancy [1], and approximately 99% of these deaths occur in developing countries [2]. Despite the current global efforts, it is estimated that only 13 countries are likely to achieve Millennium Development Goal 5, which is to reduce the maternal mortality ratio (MMR) by three-quarters between 1990 and 2015 [3]. The five major causes of the obstetric complications that are associated with maternal death are postpartum hemorrhage (PPH), sepsis, unsafe induced abortion, hypertensive disorders of pregnancy, and obstructed labor. PPH is typically defined as blood loss > 500 mL after a vaginal birth, or > 1,000 mL after a cesarean section. PPH is a leading cause of obstetric complications, accounting for 25% of maternal deaths [4], with most deaths occurring within 24–48 h of delivery [5]. Although PPH is responsible for 13.4% of maternal deaths in developed countries, it is responsible for 33.9% and 30.8% of maternal deaths in Africa and Asia, respectively [6]. Furthermore, in the developing world, the risk of maternal mortality from PPH is approximately 100-fold higher than the risk in industrialized countries, with an estimated rate of 1 in 1,000 deliveries for low income countries and an estimated rate of 1 in 100,000 deliveries for high income countries [7, 8].

1.1.2. Causes and risk factors for postpartum hemorrhage

The four major causes of primary PPH are commonly known as the “four Ts”: tone (uterine atony), trauma (genital tract trauma), tissue (retained placental tissue), and

thrombin (coagulopathies) [9]. By far, the most common cause of PPH is failed uterine contraction after delivery, which accounts for 70% of PPH cases, followed by genital tract trauma, which accounts for 20% of PPH cases [9]. Table 1.1 shows the relationship between the causes and risk factors that are associated with PPH [10-13]; the causes can be further classified according to whether they are due to spontaneous or iatrogenic factors. For example, blood loss from vaginal and cervical lacerations is considered a spontaneous factor, while blood loss from an episiotomy is considered an iatrogenic factor.

Several factors have been postulated to increase the risk of PPH among pregnant women. The most commonly cited studies that were conducted in the last two decades are listed in Table 1.2, including eight studies from developed countries and four studies from developing countries. Various study designs were used, including case-control, population-based, multicenter cluster randomized trial, and randomized clinical trial, with the study samples ranging from 207 in Nigeria to 876,614 in the USA. The lowest prevalence of PPH has been reported in Israel (0.43%) and the highest prevalence of PPH has been reported in the Netherlands (19.1%) [14-25]. For example, retained placenta and a prolonged third stage of labor are strongly associated with PPH in both developed and developing countries. Other risk factors that have been reported in developed countries include genital tract laceration, caesarean delivery, instrumental delivery, episiotomy, prolonged first and second stages of labor, preeclampsia, previous PPH, advanced maternal age, multiple pregnancy, and macrosomia. In addition, labor induction and augmentation (which are our special interests) have also been reported to increase the risk of PPH, with the lowest odds ratio (OR) in Israel (1.4) and the highest

OR in the UK (2.2) [14-16, 18, 21]. Among developing countries, antenatal hospitalization for anemia was the most important risk factor for PPH in Zimbabwe [23], while PPH was most prevalent among Nigerian women who were not administered oxytocin in the third stage of labor (the period from the birth of the baby through the delivery of the placenta) [24]. In India, women who did not complete four antenatal visits were the most likely to have PPH, while women who took iron supplements during their pregnancy were less likely to have PPH [25]. Therefore, it appears that the risk factors for PPH in developing counties have unique qualities compared to those identified in high income countries, although the information from developing countries is scarce, especially from Latin American countries [26]. Given the fact that most deaths from PPH are preventable and occur in developing countries, the identification of risk factors for PPH in developing countries is urgently needed [11].

1.1.3. Oxytocin administration during labor

As mentioned above, oxytocin administration in the third stage of labor can be used to control PPH. However, several studies have reported that the administration of oxytocin during the first stage of labor (the period from the onset of labor until the cervix is completely dilated to 10 cm) and second stage of labor (the period after the cervix is dilated to 10 cm until the baby is delivered) increases the risk of PPH. In the following sections, the dual function of oxytocin before and after childbirth and its use in the obstetric practice will be examined. Oxytocin is a hormone that is produced in the pituitary gland, and the identical synthetic form has typically been used since synthetic oxytocin's development. In its physiological role, oxytocin improves cervical ripening, and stimulates the smooth muscle of the uterus more powerfully towards the end of

pregnancy, during labor, and immediately postpartum [27].

1.1.3.1. Oxytocin in the active management of the third stage of labor

In obstetric practice, synthetic oxytocin has been used to prevent and treat PPH in the third stage of labor. As postpartum uterine atony is the leading cause of PPH, active management of the third stage of labor (AMTSL) has been widely promoted by the World Health Organization (WHO) and other international agencies, who have attempted to train healthcare professionals to prevent PPH [28, 29]. AMTSL consists of administering a prophylactic uterotonic drug, controlled cord traction (CCT), and uterine massage [30]. Oxytocin is the first drug of choice, and is administered as a prophylactic intramuscular injection of 10 international units (IU) immediately after delivery of the baby. To accommodate the increased demand for oxytocin, due to its use in AMTSL, various international organizations have called for efforts to expand its global availability.

In a practical guide for managing complications in pregnancy and childbirth, WHO has recommended that all women who are in labor should receive AMTSL to reduce the prevalence of PPH [31]. However, a number of adverse effects related to AMSTL were subsequently discovered, including high blood pressure and nausea (caused by the uterotonic agent), retained placenta, umbilical cord rupture, and uterine inversion (due to the CCT) [32]. Therefore, the WHO updated their recommendations for the prevention and treatment of PPH in 2012, indicating that the use of CCT had minimal beneficial effect on blood loss (average reduction: 11 mL) [33-35], and that skilled birth attendants in a hospital setting should consider CCT as optional practice [36]. However,

these updated recommendations regarding AMTSL have not been reflected in many countries' national guidelines. Moreover, despite the strong promotion of AMTSL during its introduction, its impact on the prevalence of PPH in developing countries has not been fully evaluated.

1.1.3.2. Oxytocin in the induction and augmentation of labor

Oxytocin is also used to induce labor (by stimulating uterine contractions prior to the onset of spontaneous labor) and to augment labor (by increasing the strength and frequency of uterine contractions during the onset of spontaneous labor). The administration of oxytocin during the first and second stages of labor has become one of the most commonly utilized medical treatments since it was first advocated by O'Driscoll et al. in Dublin, Ireland [37]. It is safe when used correctly, although overdose during oxytocin infusion is occasionally related to hyperstimulation of the uterus and uterine rupture [38]. In addition, it is associated with uterine atony during the third stage of labor, as prolonged pharmacological use of oxytocin for inducing or augmenting labor can lead to oxytocin receptor desensitization, thereby limiting the strength of the oxytocin-mediated contractions and increasing the risk of atonic PPH [39, 40]. Furthermore, a previous study has reported that the amount of oxytocin needed to induce adequate uterine retraction after caesarean delivery was 9-fold greater for women who received oxytocin during labor, compared to women who did not receive oxytocin before caesarean section [41].

After the introduction of AMTSL as standard clinical practice, the availability of oxytocin dramatically increased in low income countries, especially in their rural areas,

where the health facilities often have limited medical equipment and health personnel with knowledge regarding the induction and augmentation of labor. This situation precludes the continuous monitoring that is needed to safely induce and augment labor. In addition, many of these health facilities currently maintain sufficient stocks of oxytocin to support its routine clinical use for AMTSL. Although WHO recommends that labor induction and augmentation with oxytocin should only be implemented for a valid reason and in facilities where caesarean section can be performed [42, 43], the unnecessary and unsafe liberal use of labor induction and augmentation for low risk women at these primary health facilities has become a significant concern [44-46]. In contrast, the prevalence of PPH is relatively low in a district of Vietnam where induction and augmentation of labor is not typically used [47]. As the use of oxytocin for labor induction or augmentation is a risk factor for PPH, its liberal use in the first and second stages of labor (driven by the introduction of AMTSL) appears to pose a risk of increasing the prevalence PPH, rather than reducing it. Furthermore, previous studies have reported an increased risk of uterine atony and severe perineal or cervical laceration among women whose labors were induced or augmented [48-51].

An increased prevalence of PPH in developed countries has also been observed, along with a simultaneous increase in the induction and augmentation of labor [52-55]. For example, a Norwegian study reported an increase in severe postpartum hemorrhage (SPPH: blood loss > 1,000 mL after a vaginal birth) over a 10-year period, and the augmentation of labor was considered the most important factor that was associated with SPPH, as labor augmentation increased from 5.8% to 29.3% over the same period [56]. Trend analysis has also indicated a similar increase in the prevalence of PPH in

high resource countries, including Australia, Canada, the UK, and the USA. In these countries, a similar increase in labor induction and augmentation has been observed over that period [57]. However, there is little research from developing countries regarding the association between the risk of PPH and labor induction and augmentation, and only a few studies have investigated the exposure to oxytocin during labor induction or augmentation [58].

1.1.4. Prevalence of postpartum hemorrhage in developing countries

To analyze the risk factor for PPH in developing countries, it is necessary to clearly understand the local factors that affect the incidence of PPH. In addition, women with PPH must be identified and the prevalence of PPH must be determined. However, it appears that the relevant information has not been collected or measured properly in most developing countries. In addition, the current standard practice for assessing postpartum blood loss is visual estimation in developing countries. Using this technique, minimally-trained health care providers observe the amount of blood that is lost and make a quantitative or semi-quantitative estimate. However, previous studies have shown that this approach is inaccurate, as it underestimates the actual blood loss by up to 90% [59-67]. As a result, the reported prevalence of PPH can vary, depending on the method that was used to measure blood loss. One systematic review has analyzed 120 datasets related to PPH, and reported that the global prevalence of PPH was 6.1%, although the prevalence changed when blood loss was measured objectively (10.6%), subjectively (7.2%), or using unspecified methods (5.4%) [26]. These results suggest that it is difficult to understand the real prevalence of PPH in developing countries, where there is a paucity of data regarding accurately-measured blood loss.

In a study conducted in El Salvador, the authors reported that the prevalence of SPPH was 0.15% [68], while the official prevalence of PPH and SPPH at the National Maternity Hospital of El Salvador was 1.7% and 0.6%, respectively, as obtained from the institutional health information system (using visual estimation of blood loss). In contrast, when blood loss was quantitatively measured in a recent observational study (see Appendix 2: preliminary study 2[*]), the prevalence of PPH in the National Maternity Hospital (30.3%) was extremely high, despite the fact that all women who gave birth at this hospital had received prophylactic oxytocin during the third stage of labor. These results revealed a marked underestimation of the prevalence of PPH, and this accurate identification of women with PPH enabled an analysis of the risk factors for PPH that are specific to El Salvador.

1.1.5. Study area

El Salvador is a small Central American country with 6.2 million inhabitants, a land area of 20,742 km², and an urbanization rate of 75% (2013) [69]. The country is divided into five regions, 14 provinces, and 262 municipalities, with three tertiary public hospitals (a general hospital, a maternity hospital, and a pediatric hospital) in the capital city (San Salvador). In addition, 28 regional and provincial hospitals provide secondary medical care, and 369 health centers and 171 health posts are placed throughout the country at the municipality and community level. In El Salvador, the high density of medical facilities in a relatively small territory has contributed to improved health service access. For example, the vast majority of pregnant women (94%) have sought antenatal care at least once, and 78% have sought antenatal care at least four times.

[*] Detailed information about preliminary study is explained as Appendices 1 and 2.

Furthermore, 96% and 85% of all births are medically-assisted and facility-based, respectively [70]. In addition, El Salvador's Ministry of Health (MoH) provides free medical services at all public health facilities, and prenatal check-ups are offered at the primary, secondary, and tertiary levels. However, only secondary and tertiary hospitals provide medical services for delivery, with the exception of precipitous deliveries that are managed at the health centers. According to the health statistics provided by the MoH, El Salvador's national caesarean section rate was 28.2% in 2013 [71], and epidural or spinal anesthesia is rarely administered to relieve the pain of labor for vaginal deliveries. As no national guidelines for anesthetic delivery exist, and as instrumental deliveries (vacuum extraction and forceps) are not available in this country, the national rate of anesthetic delivery is almost 0%.

The MMR in El Salvador varies, depending on the source. According to the United Nations Children's Fund (UNICEF) [70], the adjusted MMR in 2010 was 81 per 100,000 live births, while El Salvador's MoH estimated that the MMR was 38 per 100,000 live births in 2013, which is a 71.9% decrease from the MMR in 1990 (135 per 100,000) [71]. Among the registered maternal deaths, it has been estimated that 60% and 32% of these deaths are avoidable and potentially avoidable, respectively, and that 50% are directly related to obstetric complications. In El Salvador, the major causes of maternal mortality are hypertensive disorders of pregnancy, hemorrhage, and sepsis [71], although there is no national data available regarding the percentage of maternal deaths that are attributable to hemorrhage.

1.2. Research question and objectives

The risk factors for PPH, especially the association between the level of oxytocin exposure during the early stages of labor, have not been well studied or documented. Our hypothesis was that prolonged oxytocin exposure during labor increases the risk of PPH, and we conducted a case-control study to test this hypothesis.

1.3. Structure of the thesis

This thesis reports the results of a case-control study carried out between April and June 2014 at the tertiary National Maternity Hospital in San Salvador, El Salvador. This chapter sets out the study questions and presents the general background to their formulation. Chapter 2 describes the methodologies used for the study design, data collection, and analysis. Chapter 3 focuses on the results of the study, and the main findings are brought together, summarized, and discussed in chapter 4. In chapter 5, recommendations are made regarding the prevention of PPH.

Table 1.1 Causes and risk factors associated with postpartum hemorrhage

Cause	Process	Clinical risk factors	Pathophysiology
TONE (70%) Abnormal uterine contractility	Spontaneous	Multiple gestation Polyhydramnios Macrosomia Grand multiparity	Overdistended uterus
		Prolonged labor Previous PPH Advanced maternal age	Uterine muscle fatigue
		Prolonged ROM	Chorioamnionitis
		Fibroids Placenta previa	Uterine distortion/ abnormality
	Iatrogenic	Uterine stimulants use (uterotonics) Induction of labor Augmentation of labor	Uterine rupture Uterine hyperstimulation
			Uterine muscle fatigue (desensitization of oxytocin receptor in uterine muscle)
		Uterine relaxants use Tocolyti drug/Tocolysis Anesthetic delivery	Uterine relaxation
TRAUMA (20%) Genital tract trauma	Spontaneous	Precipitous delivery Macrosomia Shoulder dystocia Malposition Malpresentation	Lacerations of cervix, vagina or perineum
		Fundal placenta Grand multiparity	Uterine inversion
	Iatrogenic	Instrumental delivery (forceps/vacuum) Episiotomy	Lacerations of vagina, perineum
		Excessive traction on umbilical cord	Uterine inversion
		Uterine stimulants use (uterotonics) Induction of labor Augmentation of labor	Laceration of cervix, vagina or perineum due to precipitous delively
TISSUE (10%) Retained product of conception	Spontaneous	Prior uterine surgery Placenta previa Succinturiate/accessory lobe	Placenta accreta/ increta/ percreta Retained placenta/ membranes
THROMBIN (1%) Abnormality of coagulation	Spontaneous	Placenta abruption, amniotic fluid embolism, preeclampsia, retained intrauterine fetal demise (IUFD)	Acquired coagulopathy
		von Willebrand disease, hemophilia, idiopathic thrombocytopenic purpura（ITP)	Inherited coagulopathy

This table was prepared with reference to previous research papers (Oyelese Y, 2010; Haeri S, 2012; Kominiarek MA, 2007; Devine PC, 2009)

Table 1.2. Previous studies related to the risk factors for postpartum hemorrhage

Authors (Publicaion year)	Study site	Study design	Case definition	Sample size	Risk factor	OR	95% CI
Waterstone et al. (2001)	South East Thames Region, London, UK	Case-control study	Blood loss ≥1,500ml, Peripartum fall in hemoglobin ≥40g/l, Blood transfusion	Case: 588 Control: 2,350 All: 48,865	Manual removal of placenta	13.12	(7.72 - 22.30)
					Emergency caesarean section	3.09	(2.29 - 4.17)
					Previous PPH	2.74	(1.69 - 4.44)
					Multiple pregnancy	2.29	(1.20 - 4.37)
					Oxytocin augmentation	1.61	(1.20 - 2.15)
					Maternal age ≥35 years	1.41	(1.03 - 1.95)
Combs et al (1991)	USA	Case-control study	Peripartum fall in hematocrito ≥10%, Blood transfusion	Case: 374 Control: 1,122 All: 9,598	Prolonged third stage	7.56	(4.23 - 13.53)
					Preeclampsia	5.02	(2.98 - 8.47)
					Episiotomy (Mediolateral)	4.67	(2.59 - 8.43)
					Previous PPH	3.55	(1.24 - 10.19)
					Multiple pregnancy	3.31	(1.03 - 10.60)
					Arrest of descent	2.91	(1.59 - 5.32)
					Lacerations	2.05	(1.45 - 2.90)
					Asian ethnicity	1.73	(1.20 - 2.49)
					Hispanic ethnicity	1.66	(1.02 - 2.69)
					Instrumental deliveries	1.66	(1.06 - 2.60)
					Augmented labor	1.66	(1.23 - 2.25)
					Episiotomy (Midlinel)	1.58	(1.12 - 2.23)
					Nulliparous	1.45	(1.05 - 2.00)
Stones et al (1993)	North West Thames Region, London, UK	Population-based study	Blood loss ≥1,000ml	498 (1.3%) All: 37,497	Placenta previa	13.1	(7.47~23.0)
					Placental abruption	12.6	(7.61~20.9)
					Retained placenta	5.15	(3.36 -7.87)
					Multiple pregnancy	4.46	(3.01~6.61)
					Induced labor	2.22	(1.67~2.96)
					Episiotoy	2.06	(1.36~3.11)
					Birth weight ≥4 kg	1.90	(1.38~2.60)
					Obesity	1.64	(1.24~2.17)
Al-Zirqi et al (2008)	Norway	Population-based study	Blood loss ≥1,500ml, Blood transfusion	3,501 (1.1%) All: 307,415	Emergency caesarean section	3.61	(3.28 - 3.95)
					Von Willebrand's disease	3.31	(1.01 - 10.85)
					Elective caesarean section	2.47	(2.18 - 2.80)
					Multiple pregnancy	2.34	(2.02 - 2.70)
					Anemia (hemoglobin <9 g/dl)	2.20	(1.63 - 3.15)
					Birth weight ≥4.5 kg	1.93	(1.71 - 2.17)
					HELLP syndrome	1.88	(1.15 - 2.84)
					Forceps	1.87	(1.40 - 2.42)
					Vacuum	1.83	(1.56 - 2.07)
					South-East Asian ethnicity	1.77	(1.48 - 2.12)
					Induced labor	1.60	(1.46 - 1.75)
					Previous caesarean delivery	1.46	(1.02 - 2.20)
					Maternal age ≥ 40 years	1.41	(1.16 - 1.74)
Sheiner et al (2005)	Israel	Population-based study	Blood loss ≥500ml	666 (0.43%) All: 154,311	Retained placenta	3.5	(2.1 - 5.8)
					Prolonged second stage	3.4	(2.4 - 4.7)
					Placenta accreta	3.3	(1.7 - 6.4)
					Lacerations	2.4	(2.0 - 2.8)
					Instrumental deliveries	2.3	(1.6 - 3.4)
					Large for gestational age	1.9	(1.6 - 2.4)
					Hypertensive disorders	1.6	(1.2 - 2.1)
					Induced labor	1.4	(1.1 - 1.7)
					Oxytocin augmentation	1.4	(1.2 - 1.7)

Continue

Authors (Publicaion year)	Study site	Study design	Case definition	Sample size	Risk factor	OR	95% CI
Bais et al (2004)	Netherlands	Population-based study	Blood loss ≥500ml	663 (19.1%) All: 3,464	Retained placenta	7.83	(3.78 - 16.22)
					Prolonged third stage	2.61	(1.83 - 3.72)
					Multiple pregnancy	2.60	(1.06 - 6.39)
					Episiotomy	2.18	(1.68 - 2.81)
					Birth weight ≥4 kg	2.11	(1.62 - 2.76)
					Laceration ≥ first degree	1.40	(1.40 - 1.87)
					West European race	1.32	(1.00 - 1.73)
Bateman et al (2010)	USA	Population-based study	According to the ICD-9 definition	25,654 (2.9%) All: 876,641	Retained placenta	4.1	(3.1. - 5.5)
					Antepartum hemorrhage	3.8	(3.0 - 4.8)
					Multiple pregnancy	2.8	(2.2 - 3.6)
					Chorioamnionitis	2.5	(1.9 - 3.6)
					Hypertensive disorders	2.5	(2.1 - 2.8)
					Polyhydramnios	1.9	(1.2 - 3.3)
					Maternal age < 20years	1.8	(1.5 - 2.2)
					Maternal age ≥40 years	1.7	(1.3 - 2.2)
					Emergency caesarean section	1.7	(1.5 - 2.0)
					Elective caesarean section	1.3	(1.1 - 1.5)
Magann et al (2005)	Australia	Population-based study	Blood loss ≥1,000ml, Blood transfusion (direct measurement of sheets, drape and sponge)	714 (5.15%) All: 13,868	Prolonged third stage	6.2	(4.6 - 8.2)
					Twin-twin transfusionsyndrome	5.1	(1.5 - 15.7)
					Compound fetal presentation	3.0	(1.1 - 7.3)
					IUFD	2.6	(1.1 - 5.7)
					Previous PPH	2.2	(1.7 - 2.9)
					Multiple pregnancy	2.2	(1.5 - 3.2)
					Forceps after unsuccessufl vacuun	1.9	(1.1 - 3.2)
					Antepartum hemorrhage	1.8	(1.3 - 2.3)
					Birth weight ≥4 kg	1.8	(1.4 - 2.3)
					Asian ethnicity	1.8	(1.4 - 2.2)
					Laceration	1.7	(1.4 - 2.1)
					Prolonged first stage	1.6	(1.0 - 1.6)
					Prolonged second stage	1.6	(1.1 - 2.1)
					Induced labor	1.5	(1.2 - 1.7)
					Epidual	1.3	(1.0 - 1.6)
					Chorioamnionitis	1.3	(1.1 - 1.7)
Sosa et al (2009)	Argentina Uruguay	Multicenter, cluster randomized trial	Blood loss ≥500ml, Blood transfusion (using drape)	1,221 (10.8%) All: 11,323	Retained placenta	6.02	(3.50 - 10.36)
					Multiple pregnancy	4.67	(2.41- 9.05)
					Birth weight ≥4 kg	2.36	(1.93 - 2.88)
					Episiotomy	1.70	(1.15 - 2.50)
					Suture	1.66	(1.11 - 2.49)
					Instrumental deliveries	1.43	(1.09 - 2.49)
					Laceration	1.23	(1.00 - 1.50)
Tsu (1993)	Zimbabwe	Population-based case control study	Blood loss ≥600ml	Case: 151 Control: 299	Antenatal hospitalisation (anemia)	4.3	(1.4 - 12.8)
					Maternal age ≥35 years	2.6	(1.2 - 5.8)
					Low parity	1.7	(1.1 - 2.7)
Selo-Ojeme et al (1997)	Nigeria	Case-control study	Blood loss ≥500ml	Case: 101 Control: 107	No AMTSL (oxytocin)	6.5	(2.5 - 10.4)
					Prolonged second stage	5.5	(2.5 - 10.2)
					Prolonged third stage	3.5	(1.4 - 5.6)
					Multiple pregnancy	2.8	(1.2 - 24.7)
Geller et al (2008)	India	Randomized trial testing oral misoprostol for	Blood loss ≥500ml	Misopro: 811 Placebo: 808	Antenatal visit <4 times	2.30	(1.50 - 3.52)
					Perineal tear	2.22	(1.30 - 3.79)
					Large birth weight	1.07	(1.23 - 1.12)
					Iron supplement	0.68	(0.48 - 0.98)

2. Methodology

2.1. Study design

2.1.1. Study structure

A case-control design was used to study the risk factors for PPH among parturient women who underwent vaginal delivery in the National Maternity Hospital, with a subsequent diagnosis of PPH (the cases). The controls met the same inclusion criteria as the cases, although without the diagnosis of PPH (see 2.2.4.). The cases and controls were compared regarding their exposure to each of the risk factors of interest, with a particular focus on their oxytocin exposure during the first and second stages of labor.

To achieve the study objectives, two preliminary studies were carried out prior to the case-control study, in an attempt to obtain accurate data regarding the amount of postpartum bleeding and the prevalence of PPH after vaginal delivery.

Preliminary study 1: A comparison of blood loss after vaginal delivery, as evaluated using visual estimation and direct measurement (Appendix 1).

Preliminary study 2: A cross-sectional study to determine the prevalence of PPH after vaginal delivery (Appendix 2).

Main study: A case-control study to analyze the risk factors for PPH, while focusing on the association between the level of oxytocin exposure during the first and second stages of labor and the risk of PPH (this study).

In this thesis, only the main study is described. The detailed information regarding preliminary studies 1 and 2 are provided as Appendices 1 and 2.

The author (E. Sasagawa) was the principal investigator for all three projects, with overall responsibility for designing the research and implementing the field work. The study was entirely designed, implemented, and analyzed as part of her Ph.D. research process, with input from her supervisors (K. Kita and C. Misago).

2.1.2. Justification for the case-control design

The choice of a case-control design, rather than a longitudinal design, was based on theoretical and logistical considerations. Case-control studies are appropriate when attempting to identify risk factors for rare diseases in a short period of time, with no risk to the subjects. In addition, the case-control design facilitates the examination of a large number of predictor variables for the disease [72]. When this study was designed (in 2013), the National Maternity Hospital's database indicated that the prevalence of PPH in 2012 among vaginal deliveries was 1.1%, and PPH was considered a rare outcome in El Salvador at that time. Moreover, in our study, suitable controls could be drawn from the same population as the cases, and any exclusion criteria or restrictions could be applied equally to the cases and controls [73].

In contrast, a longitudinal design would have required a considerably larger sample size. As the reported prevalence of PPH among vaginal delivery was relatively low (1.1% in 2012, 1.7% in 2013), only 1 or 2 cases of PPH would be detected in a sample of 100 women. Alternatively, a case-control design specifically identifies cases of PPH.

Therefore, as the amount of blood loss for a large patient population was already determined (during preliminary study 2), the identification of cases was relatively simple. Therefore, we selected controls from the participants in preliminary study 2 (Appendix 2), and we considered hospital controls to be the most appropriate choice, as they were selected from the population from which the cases were selected.

2.1.3. Study site

All studies (the preliminary and main studies) were conducted at the National Maternity Hospital, which is a top referral tertiary hospital in the field of maternal and neonatal health, and also functions as a national training center for human resources development in this field. In 2013, 11,367 women gave birth at this hospital, including 7,118 (62.2%) vaginal deliveries and 4,249 (37.4%) caesarean sections; instrumental deliveries are not performed at this hospital. For labor induction and augmentation, two kinds of uterotonics (oxytocin and misoprostol) are used during the first and second stages of labor. To prevent PPH, AMTSL is performed for 100% of women who give birth at this hospital, and oxytocin is the only uterotonic drug available for prophylactic intermuscular administration (10 IU) at the third stage of labor. When women experience PPH secondary to uterine atony, another 10 IU of oxytocin is administered via infusion. As 128,000 births took place in El Salvador during 2013 [70], the National Maternity Hospital provided 8.9% of the annual Salvadoran deliveries.

The prevailing method for measuring blood loss in the Salvadoran public hospitals (including the National Maternity Hospital) is visual estimation, and direct measurement using a scale or measuring cup is not common. In addition, the medical

and nursing records lack a designated space to record the amount of blood loss. Furthermore, although hemoglobin and hematocrit values are routinely analyzed at admission, these values are not routinely evaluated in the postpartum period. Postpartum hematological tests are typically only performed for women who are planning to undergo tubal ligation for sterilization after delivery, or when physicians express interest regarding the hematological status of women who are thought to have PPH. As no current methods existed to systematically detect cases of PPH in the public hospitals, the preliminary studies were conducted to collect the relevant information before implementing the case-control study.

2.1.4. Study period

This hospital-based study was conducted between April 1 and June 30, 2014.

2.1.5. Study team

An office was set up in the Research and Teaching Unit of the National Maternity Hospital in February 2014. A female research coordinator was recruited from the hospital staff to work on the project for approximately 4.5 months. The coordinator was an obstetrics and gynecology specialist, as well as a university lecturer with a master's degree in scientific research and relevant field research experience. In her role, she led the data collection and management, and provided day-to-day supervision at the delivery room.

In addition, three researchers were carefully selected from the hospital staff, and all three worked on the project for 3 months. One researcher was a chief of obstetrics and a

gynecology specialist, as well as a university lecturer with a master's degree in hospital administration and relevant epidemiological research experience. The two other researchers were university-trained nurses; one was a deputy director of nursing and another was head nurse of the labor and delivery ward. Both nurses had experience in the field of maternal health and good communication skills. In their roles, the three researchers provided day-to-day supervision and collected data from the medical records, using a data collection manual. This manual included detailed instructions regarding the recruitment of study participants, completing the data collection sheets, and measuring blood loss after a vaginal delivery.

Prior to the implementation of the study, a seminar regarding PPH was held at the National Maternity Hospital, and all health staff were invited. At this seminar, the purpose of the study was explained, in an attempt to gain the staff's understanding and cooperation, and all nurses and physicians who attended the vaginal deliveries were trained in postpartum blood loss measurement. Furthermore, a pilot study was conducted before the preliminary studies, and the utility of the study instruments (process and data collection sheets) were evaluated for 77 consenting women.

Once the study began, regular meetings were held between the chief of the Research and Teaching Unit, research coordinator, researchers, and principal investigator to review progress and to discuss any problems that were encountered. Furthermore, interim progress reports were presented monthly to the delivery room staff.

2.1.6. Ethical considerations

The study was approved by the Ethics Committee of the Graduate School of Medicine at the University of Tokyo, Japan (Appendix 3), The Research Committee for Health Research of the National Maternity Hospital (Appendix 4), and the Ethics Committee for Health Research of the National Maternity Hospital of El Salvador (Appendix 5).

Due to the sensitive nature of the study, all patient data were kept confidential. Before women were recruited, the aim of the study was explained using an informative leaflet (Appendix 6) and written informed consent was obtained in the local language (Spanish) (Appendix 7). When women were in the active phase of labor, the study's aims were explained verbally and written informed consent was obtained after delivery. For semiliterate or illiterate women, a thumb imprint was obtained after a physician or nurse read the consent form to the patient.

All women were assured that their participation or refusal to participate in this study would not affect their treatment or care, and that this study did not include any invasive medical practices. However, if the researchers identified any life-threatening conditions during the study period, they were instructed to immediately inform the attending physician or nurses.

2.2. Study parameters

2.2.1. Objective

This study aimed to assess the risk factors that were associated with PPH, focusing on the association between the level of oxytocin exposure during the first and second

stages of labor and the risk of PPH.

2.2.2. Sample size

A target of 230 cases and 230 unmatched controls was set, which would provide a 90% power for detecting an OR of ≥ 2 with significance set at 5% and the prevalence of exposure among the controls as 20%.

2.2.3. Inclusion and exclusion criteria

The inclusion criteria were women who consented to participate during the study period and who had undergone a vaginal delivery after uncomplicated pregnancy, at a gestational age of ≥ 35 weeks. Women with singleton or multiple pregnancies (≥ 2 fetuses), cephalic presentation, or mild complications, such as adequately controlled pre-eclampsia or diabetes, were also included.

The exclusion criteria were women who delivered by caesarean section, cases with intrauterine fetal death, the presence of antenatal hemorrhage (placenta previa, abruption, or unclassified bleeding), hematological disorders (thrombocytopenia, severe iron-deficiency anemia with hemoglobin ≤ 6 g/dL, aplastic anemia, or hemophilia), or patients with severe complications. Women who required medical treatment under anesthesia for placenta accreta or hematoma after vaginal delivery were excluded, as it was impossible to measure their blood loss once they entered to the operation room. Women who did not consent to participate in the study were also excluded.

2.2.4. Selection of cases and controls

The study was conducted using an unmatched case-control design, with cases and controls that were sequentially enrolled according to the time of delivery. The cases were defined as women who had a measured postpartum blood loss of ≥ 500 g. The controls were women who met the inclusion criteria, had a measured postpartum blood loss of < 400 g, and did not receive a blood transfusion after delivery.

The exclusion of patients with a measured blood loss of 400–499 g allowed a clear separation of patients with PPH from those who did not have PPH, and this distinction enhanced the quantification of PPH's effect. In practice, the total amount of bleeding is a continuous variable, and it is difficult to clearly divide patients into groups based on the presence or absence of PPH, as false PPH-negative cases are difficult to rule out, given the inherent underestimation of the estimation method that was used in the preliminary study (Appendix 2). For example, blood that fell to the floor or was absorbed into the protective gown is not included in that method. Moreover, when babies were born with low Apgar scores (i.e., requiring resuscitation), it was impossible to begin the blood collection immediately after childbirth.

2.2.5. Study variables

The main outcome measure was PPH, which was defined as blood loss of ≥ 500 g after a vaginal delivery, according to the traditional definition proposed by WHO in 1990 [74]. The explanatory variables included socio-demographic characteristics, obstetric and pregnancy history, duration of labor, location of the bleeding site, neonatal characteristics, and birth outcomes. In addition, the level of exposure to oxytocin during

the first and second stages of labor was of special interest.

In the National Maternity Hospital, a uniform infusion of 5 mIU/mL is used, based on a concentration of 5 units of oxytocin in 1,000 mL of saline solution. According to the hospital regulations, the initial rate was set at 2.5 mIU/min, with an increase of 2.5 mIU/min every 30 min, up to a maximum rate of 20 mIU/min (until regular contractions began or labor progressed). The rate of oxytocin infusion was managed by gravity-fed infusion, rather than by an infusion pump, although the infusion rate was periodically observed by the physicians. The time at which the oxytocin infusion was started was recorded, and the time and dose for each dose change was also noted. The variables related to oxytocin exposure included the total dose of oxytocin, maximal infusion rate, duration of oxytocin infusion, and time at the maximal infusion rate. The quantitative data regarding oxytocin administration was categorized as low or high levels of oxytocin exposure, using the 75th percentile of their distribution in the control group (blood loss < 400 g).

2.2.6. Data collection procedures

Data was collected from the patient's medical records using a data collection sheet (Appendix 8), and the medical records and the delivery log book were reviewed carefully by the research coordinator and researchers before the patients were discharged. To ensure a high degree of accuracy for each item on the data collection sheet, all discrepancies were reviewed, and the unrecorded information was collected by directly speaking with the attending physicians, nurses, and patients (if necessary). Data regarding transfusion and postpartum hematocrit levels were double-checked by

reviewing the transfusion registration book from the Blood Bank Unit and the hematological data from the Clinical Laboratory Unit of the National Maternity Hospital.

2.2.7. Data analysis

All data were analyzed using SPSS for Windows version 17.0 (IBM/SPSS Inc., Chicago, IL). The initial descriptive analyses were used to evaluate the characteristics of participants. Next, the case and control groups were compared using the chi-square test for categorical variables. A p-value of < 0.05 was considered statistically significant, and all tests were two-tailed.

For the oxytocin related variables (total dose, maximal infusion rate, duration of infusion, and time at the maximal infusion rate), a value of 0 was entered for subjects who did not receive oxytocin. In addition, their characteristics were compared using the t test for continuous variables. Variables were reported as percentages, mean ± standard deviation (SD), or median and the interquartile range, as appropriate. To verify the dose-response relationship between the level of oxytocin exposure and the risk of PPH, linear trend analysis was performed using the Cochran-Armitage trend test. Multicollinearity between the possible independent variables was examined by assessing their variance inflation factor (VIF). Only variables with a VIF value < 10 were selected as independent variables and included in the multivariate analysis.

Multivariate analyses were performed to adjust for the variables that were identified as potential confounders in the bivariate analyses, due to the obvious intercorrelation

between the variables. As the dependent variable was dichotomous (i.e., having PPH or not having PPH), and an unmatched case-control design was employed, binominal logistic regression was performed, and the variables with a significant bivariate association with PPH ($p < 0.05$ in the chi-square test) were selected as possible independent variables for inclusion in the logistic models. Two regression models were used to estimate the risk of PPH. The first step was a simultaneous method in which all variables were included at the same time, and the second step was a backward stepwise selection method with coefficient recalculation at each step for the potential confounding variables. The final model included all the clinical effects of interest with the best fit for the data.

3. Results

3.1. Study participants

During the study period, there were 2,684 deliveries at the National Maternity Hospital, including 1,591 (59.3%) vaginal deliveries and 1,093 (40.7%) caesarean sections. Of the 1,591 vaginal deliveries, 258 women were excluded from this study: 134 with a gestational age < 35 weeks, 105 who had severe obstetric complications, 17 who experienced intrauterine fetal death, and 2 who required medical treatment under anesthesia after vaginal delivery. Therefore, the remaining 1,333 women met the inclusion criteria for this study (Figure 3.1). Among the 1,333 eligible patients, 463 (34.7%) women were not approached to participate in the study by the hospital staff, and all 870 (65.3%) women who were recruited by hospital staff agreed to participate in the study. During the same time period, four maternal deaths were recorded, although these women did not have PPH, and only one maternal death (caused by sepsis) was included in the study. The procedures above were conducted as a part of preliminary study 2 to detect births that were complicated by PPH, and the detailed information is described in Appendix 2.

Among the 870 women who agreed to participate, 264 women experienced blood loss ≥ 500 g after vaginal delivery, including 43 women who lost ≥ 1,000 g of blood, giving a prevalence of PPH and SPPH of 30.3% and 4.9%, respectively. However, one patient was excluded due to the lack of identifiable information, which was impossible to access via her medical records, leaving 263 women who were selected as the cases.

Among the 870 participants, 606 women experienced blood loss < 500 g, and 125

women who lost 400 – 499 g of blood were excluded per our selection protocol (Section 2.2.4.). Among the 481 remaining women, 263 controls were sequentially selected according to the time of delivery.

3.2. Characteristics of the study participants and their infants

3.2.1. Socio-demographic characteristics

Selected socio-demographic characteristics of the 526 cases and controls enrolled in the study are shown in Table 3.1. The study participants typically had a low socio-economic status. More than half of the women were 20 to 34 years old (58.4%), 34.8% were < 20 years old, and 6.8% were > 35 years old. Most women lived in the San Salvador province (77.6%) and in urban areas (84.9%). According to the body mass index (BMI) classification for pregnant women (as was proposed by the Institute of Medicine) [75], the majority of the women (75.5%) were overweight or obese (BMI $\geq$ 25 kg/m^2), and 24.5% were underweight or normal weight (BMI < 25 kg/m^2).

There were no statistically significant differences when the socio-demographic characteristics of the case and control groups were compared.

3.2.2. Obstetric and pregnancy history

The women's obstetric and pregnancy histories are listed in Table 3.2. Parity was divided into three categories: primipara women, 1–3 parous women, and $\geq$ 4 parous women. The case group contained more primipara women (61.8%) compared to the control group (50.6%). However, 1–3 parous women in the case group were less likely to experience PPH (36.9%) compared to those in the control group (40.5%), and $\geq$ 4

parous women were also less likely to experience PPH (1.5%) compared to those in the control group (3.4%) ($p = 0.006$). The majority of women (89.7%) experienced labor at term (gestational age: 37–41 weeks), 8.6% were premature (35–36 weeks), and 1.7% experienced post-term delivery (42 weeks). Most women (86.1%) were scheduled for childbirth in advance, and 13.9% were referred from other health facilities. However, significantly more women in the case group were referred (17.6%) compared to the control group (10.3%) ($p = 0.015$). Very few women (0.6%) had a previous caesarean section. Most women (81.1%) had received at least four prenatal check-ups, per the WHO recommendations, and 99.6% had received at least one antenatal check-up. In El Salvador, hemoglobin testing is obligatory at two antenatal medical examinations, one before to the 20th week of gestation and one after the 20th week of gestation. Hemoglobin levels < 11.0 g/dL were considered to indicate anemia, and 6.5% and 7.9% of women had anemia before and after 20 weeks of gestation, respectively. Furthermore, hemoglobin and hematocrit (anemia: < 33%) testing were also mandatory at the time of admission. On admission, 11.5% of women had hemoglobin levels of < 11.0 g/dL, and 10.2% of women had hematocrit levels of < 33.0%. Chorioamnionitis was also observed in the case (3.8%) and control (3.4%) groups. As only one parturient woman in the case group gave birth to twins, the association between multiple pregnancies and the risk of PPH was not analyzed.

In summary, significantly fewer women in the case group were multiparous ($p = 0.006$), compared to in the control group. In addition, more women were referred from another health facility ($p = 0.015$) in the case group when the obstetric and pregnancy histories of the case and control groups were compared.

3.2.3. Duration of labor

The categories for duration of labor are shown in Table 3.3, and the continuous variables were grouped into two or three categories. Although the average length of labor depends on parity, the gathered data of primipara and multipara women were utilized in this study. The mean length and limits (95th percentile) of the first stage of labor for primipara women are 8.1 h and 16.6 h, and the mean length and limits for multipara women are 5.7 h and 12.5 h [76, 77]. Based on that data, shorter labor was defined as < 8 h for primipara women and < 5 h for multipara women, while prolonged labor was defined as ≥ 16 h for primipara women and ≥ 12 h for multipara women. A prolonged second or third stage of labor was defined as ≥ 60 minutes and ≥ 30 minutes, respectively, for both primipara and multipara women, per the WHO definitions. The duration of expulsive efforts, and the duration of postpartum medical procedures for suturing or inspection were separated as normal or prolonged at the 75th percentile.

Fewer women in the case group had a shorter first stage of labor (19.2%) compared to the control group (21.5%), although more women in the case group had a prolonged first stage of labor (30.4%) compared to the control group (26.9%). A prolonged second stage of labor was observed in 1.0% of the case and control groups. A prolonged third stage of labor was not observed in the case group, although 1.5% of women in the control group experienced a prolonged third stage. More women in the case group had a prolonged expulsive effort (≥ 14 min, 27.0%) compared to the control group (25.6%). In addition, prolonged postpartum medical procedures (≥ 50 min) were more significantly common in the case group (29.1% of women) compared to the control group (16.7% of women) ($p = 0.001$).

In summary, there was statistically significant difference in the prevalence of prolonged postpartum medical procedures for the case and control groups ($p = 0.001$).

3.2.4. Location of the bleeding site

The location of the bleeding site indicated where active bleeding was present, and the location was classified into four anatomic regions: uterine body, cervix, vagina, and perineal area. In this study, to distinguish between bleeding from a perineal tear and from an episiotomy (as both involve bleeding from the perineal area), the diagnostic name was used instead of the anatomic location. These locations are listed in Table 3.4. Uterine atony was confirmed in 5.7% of the study sample, and significantly more women in the case group had uterine atony (11.0%) compared to the control group (0.4%) ($p < 0.001$). In addition, significantly more women in the case group underwent episiotomy (65.9%) compared to the control group (51.5%) ($p = 0.001$). Perineal tears were categorized as first-degree or second- to fourth-degree. A first-degree tear is a laceration that is limited to the superficial perineal skin or vaginal mucosa, and it heals naturally in many cases. However, a second-degree tear is a laceration that extends beyond perineal muscles, and requires suturing. More women in the case group had first-degree perineal tears (18.3%) compared to the control group (15.7%). In addition, significantly more women in the case group had second- to fourth-degree perineal tears (6.1%) compared to the control group (1.1%) ($p = 0.006$). Vaginal laceration was also observed significantly more often among women in the case group (8.2%) compared to the control group (2.3%) ($p = 0.003$). Lastly, more women had cervical tears in the case group (1.9%) compared to the control group (1.5%), although the difference was not statistically significant.

In summary, statistically significant differences in uterine atony ($p < 0.001$), the prevalence of episiotomy ($p = 0.001$), perineal tears ($p = 0.006$), and vaginal laceration ($p = 0.003$) were observed when location of the bleeding site for the case and control groups were compared.

3.2.5. Neonatal characteristics

The association between PPH and the neonatal characteristics is shown in Table 3.5, with the continuous variables (birth weight, height, and head circumference) converted into categorical variables. Birth weight was divided into three categories: macrosomia (≥ 4,000 g), normal birth weight (2,500–3,999 g), and low birth weight (LBW) (< 2,500 g). The 90th percentiles for birth height and head circumference are widely used as cutoff points (≥ 51 cm for birth height and ≥ 35 cm for head circumference) to define a large newborn.

More than half of all newborns were female (50.4%). Regarding birth weight, more women in the case group had a newborn with macrosomia (2.3%) compared to the control group (0.4%). In contrast, significantly fewer LBW newborns were observed in the case group (1.9%) compared to the control group (9.5%) ($p < 0.001$). Tall newborns were significantly more frequent in the case group (24.7%) compared to the control group (14.9%) ($p = 0.005$). Lastly, more women in the case group had newborns with a large head circumference (53.6%) compared to the control group (46.4%), although the difference was not significant.

In summary, there were statistically significant differences in the birth weight ($p <$

0.001) and the birth height (p = 0.005) when neonatal characteristics of the case and control groups were compared.

3.2.6. Birth outcomes

The analysis of the association between birth outcomes and the risk of PPH is shown in Table 3.6. Twelve women (2.3%) received a blood transfusion after delivery, with significantly more cases receiving transfusions (n = 11, 4.2%) compared to controls (n = 1, 0.4%) (p = 0.003). The patient in the control group required the transfusion due to severe anemia, as her hematocrit level was 28.1% at admission and 21.5% in the postpartum period, with a total blood loss of 284 g. In addition, significantly more women in the case group had anemia (hematocrit < 33%: 53.5%) compared to the control group (31.9%) (p = 0.017). Surprisingly, among the 526 participants, postnatal hematocrit testing was only performed for 133 (25.4%) women. Specifically, among the 263 women who had PPH, 86 (32.7%) underwent hematological tests during the postpartum period. However, only 26 of the 43 women with SPPH (60.5%) were tested for anemia, meaning that 39.5% of women with SPPH did not undergo hematological testing during the postpartum period (data not shown).

3.2.7. Summary of the bivariate analyses

Bivariate analysis identified 11 factors (out of 30 possible variables) that had significant or marginal associations with PPH (p < 0.05). These included patients who were referred from another health facility, a prolonged postpartum medical procedure, uterine atony, episiotomy, second- to fourth-degree perineal tears, vaginal laceration, and birth height ≥ 51 cm. However, multipara women and women who delivered LBW neonates

were less likely to have PPH. After vaginal delivery, significantly more women in the case group received a blood transfusion and had anemia.

In the logistic regression analysis, four variables were excluded (patients who were referred from another health facility, a prolonged postpartum medical procedures, blood transfusion, and postpartum anemia). Women who were referred from another health facility were excluded, as their referral implies a high-risk status that required special attention at the study hospital, making it impossible to accurately evaluate their risk factors. The remaining three variables were excluded because they were not risk factors, as they are consequences of PPH.

Prior to the logistic regression analysis, dummy variables were created for variables with three categories (parity, perineal tears, and birth weight), and the category with the greatest frequency was designed as the reference category. Furthermore, the VIF of the following variables (parity, uterine atony, episiotomy, perineal tears, vaginal laceration, birth weight, and birth height) and the oxytocin-related variables (augmentation of labor, oxytocin total dose, maximal infusion rate, duration of oxytocin infusion, and time at the maximal rate of infusion) were assessed. The VIF values for all variables were < 10, therefore it was not necessary to address their multicollinearity, and all variables were used as independent variables for the binominal logistic regression analysis.

3.3. Oxytocin administration during the first and second stages of labor and the risk of postpartum hemorrhage

3.3.1. Induction and augmentation of labor

Among the 526 participants, 9 (1.7%) women experienced induction of labor, 104 (19.8%) women experienced augmentation of labor, and 413 (78.5%) women gave birth spontaneously. In the National Maternity Hospital, two kinds of uterotonics are used (oxytocin and misoprostol); labor was induced using oxytocin for 2 women and misoprostol was used for 7 women. However, oxytocin was the only drug that was used for all 104 (19.8%) women whose labor was augmented.

For our analysis, the induced labors could not be combined with the augmented labors, as a greater amount of oxytocin was inevitably required to induce vaginal delivery. Therefore, as only two labors were induced using oxytocin (our variable of interest), all 9 women with induced labors were excluded from the analysis. Thus, data from 257 women in the case group and 260 women in the control group were analyzed.

Prior to the multivariate analysis, we examined the possibility that our analysis may have been biased by the initial condition of cervix, which is known as cervical ripening. Because the ripeness of the cervix is an important factor in predicting the progress of labor augmentation, it could be a potential confounding factor for our analysis [78]. Therefore, the association between PPH and the initial cervical dilatation was assessed among 104 women, and the risk of PPH was compared according to the cervical dilatation status (0–1 cm vs. $\geq$ 2 cm, 0–2 cm vs. $\geq$ 3cm, or 0–3 cm vs. $\geq$ 4 cm). This analysis revealed no statistically significant differences between the case and control groups (data not shown), and therefore we concluded that cervical ripening status was not a relevant confounder for our analysis.

3.3.2. Augmentation of labor and the risk of postpartum hemorrhage

Oxytocin was administered during labor to 24.1% (62/257) of the cases and 16.2% (42/260) of the controls, and the independent effect of oxytocin-augmented labor on the risk of PPH was tested. Crude analysis revealed that oxytocin administration occurred significantly more often for women with PPH compared to the controls (crude OR: 1.65, 95% CI: 1.07–2.55). However, this association disappeared after controlling for the confounding effects of the variables that were significantly associated with PPH in the bivariate analysis (parity, uterine atony, episiotomy, perineal tears, vaginal tear, birth weight, and birth height) (adjusted OR: 1.50, 95% CI: 0.91–2.46) (Table 3.7).

3.3.3. Total dose of oxytocin

The association between the quantified oxytocin exposure and the risk of PPH was also assessed. Among the 104 women whose labor was augmented, the total oxytocin dose ranged from 0.05 IU to 8.7 IU for the cases (mean: 2.8 ± 2.3 IU), compared to a range of 0.2 IU to 6.8 IU for the controls (mean: 2.0 ± 1.8 IU). Although the cases received a higher mean dose, the difference was not statistically significant ($p = 0.054$). In addition, the effect of each level of oxytocin exposure on the risk of PPH was compared with the risk for women who did not receive oxytocin during labor. While the crude analysis revealed a statistically significant linear trend ($p = 0.015$ for trend), after controlling for the potential confounders, no significant linear trend in total dose was observed ($p = 0.104$ for trend). Furthermore, although the high level of exposure in the total dose of oxytocin was significant associated with an elevated risk of PPH (crude OR: 2.48, 95% CI: 1.11–5.58) for a total dose of ≥ 3 IU , after controlling for the potential confounding factors, no total dose-related association with the risk of PPH was observed, with an

adjusted OR of 1.41 (95% CI: 0.81–2.45) for a total oxytocin dose of < 3 IU and 1.79 (95% CI: 0.70–4.53) for ≥ 3 IU dose.

3.3.4. Maximal infusion rate of oxytocin

The maximal infusion rate ranged from 2.5 mIU/min to 20 mIU/min for the cases (mean rate: 12.3 ± 5.5 mIU/min), with an identical range of 2.5 to 20 mIU/min for the controls, although the mean rate was slightly lower for the controls (10.8 ± 5.6 mIU/min). The cases were exposed to more oxytocin according to the maximal infusion rate, although this increase was not significantly different ($p = 0.354$). Although the crude analysis revealed a statistically significant linear trend ($p = 0.019$ for trend), the trend was no longer significant after controlling for the potential confounding factors ($p = 0.095$ for trend). While the high level of exposure at the maximal infusion rate of oxytocin was significant associated with an increased risk of PPH (crude OR: 2.24, 95% CI: 1.06–4.73) for a total dose of ≥ 15 mIU/min, all levels of oxytocin exposure at the maximal infusion rate were not significantly associated with an increased risk of PPH, with an adjusted OR of 1.37 (95% CI: 0.77–2.43) for a maximal infusion rate of < 15 mIU/min and 1.81 (95% CI: 0.79–4.18) for ≥ 15 mIU/min.

3.3.5. Duration of oxytocin infusion

The duration of oxytocin infusion ranged from 80 to 590 min for the cases (mean: 308 ± 145 min), compared to a range of 55 to 518 min for the controls (mean: 229 ± 123 min). The cases received significantly longer oxytocin infusions ($p = 0.004$), and a significant linear trend was observed in the duration of oxytocin infusion ($p = 0.090$ for trend). Although the high level of exposure in the duration of oxytocin infusion was

significantly associated with an increased risk of PPH (crude OR: 2.64, 95% CI: 1.27–5.49) for infusions lasting ≥ 300 min (≥ 5 h), the risk of PPH disappeared after controlling for the confounding factors, with an adjusted OR of 1.22 (95% CI: 0.67–2.21) for an infusion lasting < 300 min (< 5 h) and1.98 (95% CI: 0.89–4.43) for an infusion lasting ≥ 300 min (≥ 5 h).

3.3.6. Time at the maximal infusion rate of oxytocin

The time at the maximal infusion rate ranged from 20 to 540 min for the cases (mean: 145 ± 110 min), compared to a range of 25 to 315 min for the controls (mean: 100 ± 80 min). The cases received significantly longer infusions at the maximal rate (p = 0.019), and a significant linear trend was observed after controlling for the potential confounders (p = 0.048 for trend). The high levels of oxytocin exposure for time at the maximal infusion rate were significantly associated with an increased risk of PPH at ≥ 120 min (≥ 2 h) of exposure time (crude OR: 2.79, 95% CI: 1.39–5.61). After adjusting for the confounding factors, the high level of oxytocin exposure was significantly associated with an increased risk of PPH (adjusted OR: 2.29, 95% CI: 1.05–5.01). No significant association was observed between the risk of PPH and the low level of oxytocin exposure, with and adjusted OR of 1.16 (95% CI: 0.64-2.12) for <120 min (< 2 h) of exposure.

3.4. Variables that independently increased the risk of postpartum hemorrhage

In the final logistic regression model, which used the backward stepwise selection method, several variables were independently related to an increased risk of PPH. These significant associations were observed between the risk of PPH and uterine atony

(adjusted OR: 31.61, 95% CI: 3.88–257.27), second- to fourth-degree perineal tears (adjusted OR: 5.12, 95% CI: 1.40–19.16), vaginal laceration (adjusted OR: 3.26, 95% CI: 1.22–8.75), episiotomy (adjusted OR: 1.95, 95% CI: 1.29–2.94), LBW (adjusted OR: 0.27, 95% CI: 0.10–0.74), and multipara ≥ 4 (adjusted OR: 0.12, 95% CI: 0.02–0.79) (Table 3.8).

3.5. Classification of the causes of postpartum hemorrhage

Lastly, the direct causes of PPH among the 263 cases were classified. Among these subjects, the primary etiology of PPH was traumatic bleeding (including perineal tears, cervical laceration, vaginal laceration, and episiotomy) in 200 (76.0%) cases, followed by a combination of uterine atony and genital tract trauma in 23 (8.7%) cases, and atonic bleeding in 6 (2.3%) cases. In 34 (12.9%) cases, the etiology of PPH was unspecified.

Figure 3.1. Study flow-diagram

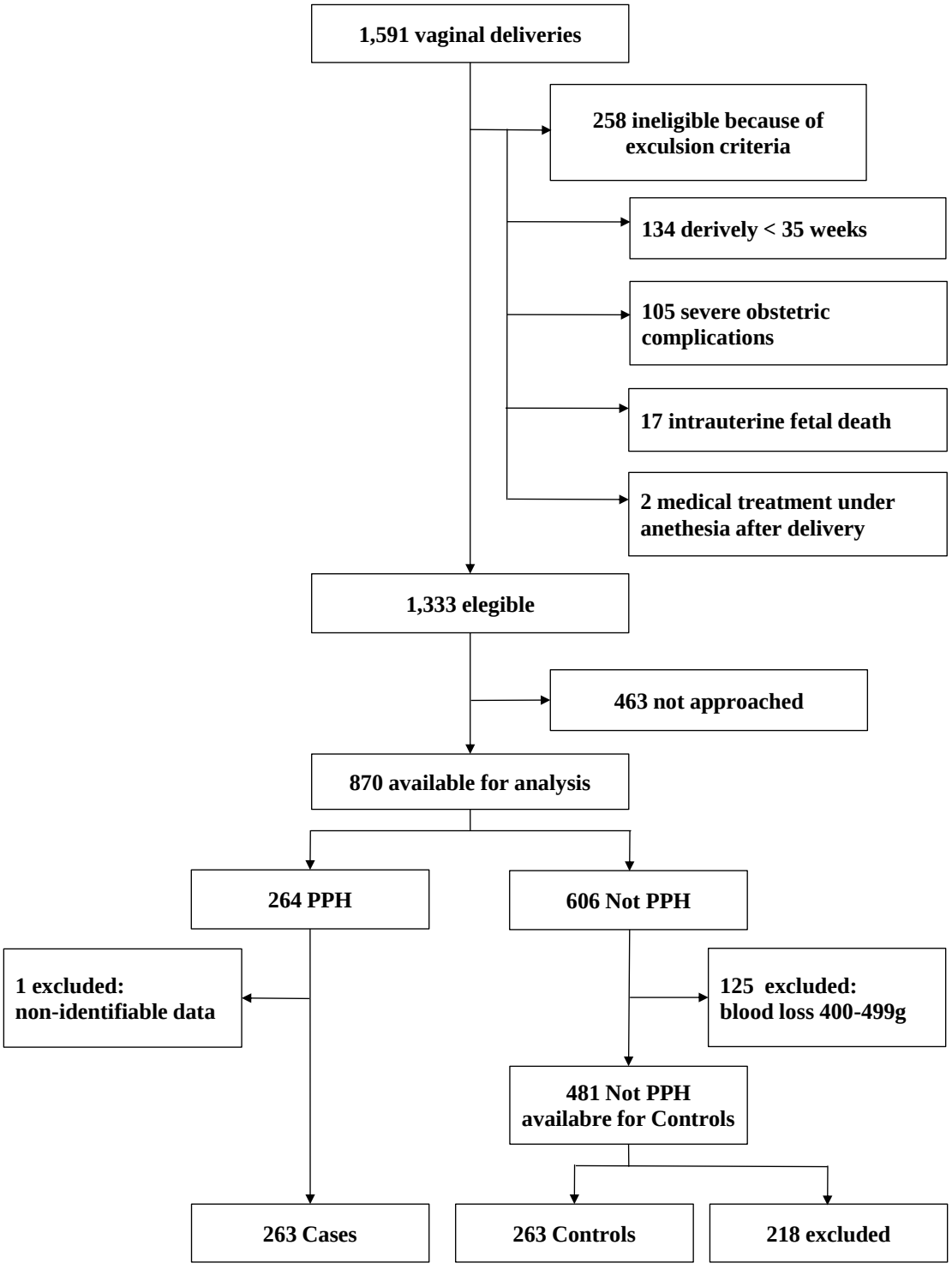

Table 3.1. Socio-demographic characteristics associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Maternal age							
< 20 years	93	35.4%	90	34.2%	183	34.8%	0.225
20 - 34 years	157	59.7%	150	57.0%	307	58.4%	
≥ 35 years	13	4.9%	23	8.7%	36	6.8%	
Province							
San Salvador province	204	78.2%	199	77.1%	403	77.6%	0.778
Other provinces	57	21.8%	59	22.9%	116	22.4%	
Residence area							
Urban	224	85.8%	219	83.9%	444	84.9%	0.541
Rural	37	14.2%	42	16.1%	79	15.1%	
BMI							
Underweight/Normal: < 25	45	23.2%	45	26.0%	90	24.5%	0.531
Overweight/Obesity: ≥ 25	149	76.8%	128	74.0%	277	75.5%	

Table 3.2. Obstetric and pregnancy history associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Parity							
Primipara	162	61.6%	133	50.6%	295	56.1%	0.006 *
1-3 parous	97	36.9%	116	44.1%	213	40.5%	
≥ 4 parous	4	1.5%	14	5.3%	18	3.4%	
Gestational age							
Premature: 35-36 weeks	22	8.4%	23	8.7%	45	8.6%	0.935
At term: 37-41 weeks	236	90.1%	235	89.4%	471	89.7%	
Post-term: ≥ 42 weeks	4	1.5%	5	1.9%	9	1.7%	
Maternal transport from other health facilities							
Yes	46	17.6%	27	10.3%	73	13.9%	0.015 *
No	215	82.4%	236	89.7%	451	86.1%	
Previous caesarean section							
Yes	2	0.8%	1	0.4%	3	0.6%	0.563
No	261	99.2%	262	99.6%	523	99.4%	
Prenatal checkup							
0-3 times	38	16.2%	51	21.7%	89	18.9%	0.157
≥4 times	197	83.8%	184	78.3%	381	81.1%	
Hemoglobin before the 20th week							
Anemia: < 11 g/dL	178	92.7%	169	94.4%	24	6.5%	0.505
No anemia: ≥ 11 g/dL	14	7.3%	10	5.6%	347	93.5%	
Hemoglobin after the 20th week							
Anemia: < 11 g/dL	127	91.4%	119	93.0%	21	7.9%	0.627
No anemia: ≥ 11 g/dL	12	8.6%	9	7.0%	246	92.1%	
Hemoglobin on admission							
Anemia: < 11 g/dL	199	88.4%	210	88.6%	53	11.5%	0.956
No anemia: ≥ 11 g/dL	26	11.6%	27	11.4%	409	88.5%	
Hematocrit on admission							
Anemia: < 33 %	201	88.9%	214	90.7%	47	10.2%	0.536
No anemia: ≥ 33 %	25	11.1%	22	9.3%	415	89.8%	
Chorioamnionitis							
Yes	10	3.8%	9	3.4%	19	3.6%	0.815
No	253	96.2%	254	96.6%	507	96.4%	

* Chi-square test statistically significant ($p < 0.05$)

Table 3.3. Duration of labor associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Duration of the first stage of labor †							
Shorter labor	46	19.2%	52	21.5%	98	20.3%	0.642
Normal labor	121	50.4%	125	51.7%	246	51.0%	
Prolonged labor	73	30.4%	65	26.9%	138	28.6%	
Duration of the second stage of labor							
≥ 60 min	5	1.0%	5	1.0%	10	1.0%	0.400
< 60 min	257	98.1%	257	98.1%	514	98.1%	
Duration of the third stage of labor							
≥ 30 min	0	0%	4	1.5%	4	0.8%	0.141
< 30 min	262	100%	258	98.5%	520	99.2%	
Duration of expulsive efforts							
≥ 14 min	67	27.0%	65	25.6%	132	26.3%	0.717
< 14 min	181	73.0%	189	74.4%	370	73.7%	
Duration of medical procedure							
≥ 50 min	73	29.1%	42	16.7%	115	22.9%	0.001 *
< 50 min	178	70.9%	209	83.3%	387	77.1%	

* Chi-square test statistically significant ($p < 0.05$)

† Shorter labor: <8 hours for primipara and <5 hours for multipara.
Prolonged labor: ≥16 hours for primipara and ≥12 hours for multipara.

Table 3.4. Location of the bleeding site associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Uterine atony							
Yes	29	11.0%	1	0.4%	30	5.7%	< 0.001*
No	234	89.0%	262	99.6%	496	94.3%	
Episiotomy							
Yes	172	65.9%	135	51.5%	307	58.7%	0.001 *
No	89	34.1%	127	48.5%	216	41.3%	
Perineal tear							
No	198	75.6%	217	83.1%	415	79.3%	0.006 *
1st degree	48	18.3%	41	15.7%	89	17.0%	
≥2nd degrees	16	6.1%	3	1.1%	19	3.6%	
Vaginal laceration							
Yes	19	8.2%	6	2.3%	25	5.1%	0.003 *
No	213	91.8%	256	97.7%	469	94.9%	
Cervical laceration							
Yes	5	1.9%	4	1.5%	9	1.7%	0.741
No	255	98.1%	255	98.5%	510	98.3%	

* Chi-square test statistically significant ($p < 0.05$)

Table 3.5. Neonatal characteristics associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Sex							
Male	134	51.1%	126	48.1%	260	49.6%	0.485
Female	128	48.9%	136	51.9%	264	50.4%	
Birth weight							
Low birth weight: < 2,500 g	5	1.9%	25	9.5%	30	5.7%	< 0.001 *
Normal: 2500 - < 4,000 g	252	95.8%	236	90.1%	488	93.0%	
Macrosomia: ≥ 4,000 g	6	2.3%	1	0.4%	7	1.3%	
Birth height							
≥ 51 cm	65	24.7%	39	14.9%	104	19.8%	0.005 *
< 51 cm	198	75.3%	223	85.1%	421	80.2%	
Birth head circumference							
≥ 35 cm	67	53.6%	58	46.4%	125	24.0%	0.319
< 35 cm	192	74.1%	204	77.9%	396	76.0%	

* Chi-square test statistically significant ($p < 0.05$)

Table 3.6. Birth outcomes associated with postpartum hemorrhage

	Case		Control		Total		*p*
	n=263	%	n=263	%	n=526	%	
Blood transfusion							
Yes	11	4.2%	1	0.4%	12	2.3%	0.003 *
No	252	95.8%	262	99.6%	514	97.7%	
Postpartum hematocrit							
Anemia: < 33 %	46	53.5%	15	31.9%	61	45.9%	0.017 *
No anemia: ≥ 33 %	40	46.5%	32	68.1%	72	54.1%	

* Chi-square test statistically significant ($p < 0.05$)

Table 3.7. Association between oxytocin administration during the early stages of labor and the risk of postpartum hemorrhage *

	Case n=257	%	Control n=260	%	Total n=517	%	*t* test *p*	Crude OR	95% CI	*p*	Adjusted (Model 1) ‡ OR	95% CI	*p*	Adjusted (Model 2) § OR	95% CI	*p*
Augmentation of labor																
No	195	75.9%	218	83.8%	413	79.9%		Ref			Ref			Ref		
Yes	62	24.1%	42	16.2%	104	20.1%		1.65	(1.07 - 2.55)	0.024	1.50	(0.92 - 2.47)	0.107	1.50	(0.91 - 2.46)	0.109
Oxytocin total dose ‖																
Mean (SD) †	2.8 (2.3)		2.0 (1.8)		2.5 (2.1)		0.054									
Median (25th, 75th pc) †	2.1 (1.1, 4.1)		1.5 (0.7, 2.9) 5.3		1.9 (0.9, 3.2)											
(min -max)	(0.05 - 8.7)		(0.2 - 6.8)		(0.05 - 8.7)											
No oxytocin	195	76.5%	218	83.8%	413	80.2%		Ref		0.015	Ref		0.123	Ref		0.104
< 3IU	40	15.7%	33	12.7%	73	14.2%		1.36	(0.82 - 2.23)		1.40	(0.80 - 2.44)		1.41	(0.81- 2.45)	
≥ 3IU	20	7.8%	9	3.4%	29	5.6%		2.48	(1.11 - 5.58)		1.72	(0.67 - 4.41)		1.79	(0.70 - 4.53)	
Maximal infusion rate ‖																
Mean (SD) †	12.3 (5.5)		10.8 (5.6)		11.5 (5.5)		0.354									
Median (25th, 75th pc) †	10 (7.5, 17.5)		10 (7, 15) 20		10.0 (7.5, 15.6)											
(min -max)	(2.5 - 20.0)		(2.5 - 20.0)		(2.5 - 20.0)											
No oxytocin	195	76.5%	218	83.8%	413	80.2%		Ref			Ref			Ref		
< 15mIU/min	38	14.9%	31	11.9%	69	13.4%		1.37	(0.82 - 2.29)	0.019	1.35	(0.76 - 2.41)	0.109	1.37	(0.77 - 2.43)	0.095
≥ 15mIU/min	22	8.6%	11	4.2%	33	6.4%		2.24	(1.06 - 4.73)		1.78	(0.77 - 4.13)		1.81	(0.79 - 4.18)	
Total time of oxytocin infusion ‖																
Mean (SD) †	308 (145)		229 (123)		276 (141)		0.004									
Median (25th, 75th pc) †	267 (203, 412)		193 (139, 331) 424		240 (160, 390)											
(min -max)	(80 - 590)		(55 - 518)		(55 - 590)											
No oxytocin	195	76.2%	218	83.8%	413	80.0%		Ref			Ref			Ref		
< 300 min (<5 hr)	35	13.7%	31	11.9%	66	12.8%		1.26	(0.75 - 2.12)	0.008	1.22	(0.672 - 2.22)	0.089	1.22	(0.67 - 2.21)	0.090
≥ 300 min (≥5 hr)	26	10.2%	11	4.2%	37	7.2%		2.64	(1.27 - 5.49)		1.99	(0.89 - 4.45)		1.98	(0.89 - 4.43)	
Time at maximal infusion rate ‖																
Mean (SD) †	145 (110)		100 (80)		127 (101)		0.019									
Median (25th, 75th pc) †	118 (60, 201)		64 (44, 160) 244		90 (50, 180)											
(min -max)	(20 - 540)		(25 - 315)		(20 - 540)											
No oxytocin	195	76.5%	218	83.8%	413	80.2%		Ref			Ref			Ref		
< 120 min (<2 hr)	30	11.8%	30	11.5%	60	11.7%		1.12	(0.65 - 1.92)	0.006	1.16	(0.63 - 2.13)	0.059	1.16	(0.64 - 2.12)	0.048
≥ 120 min (≥2 hr)	30	11.8%	12	4.6%	42	8.2%		2.79	(1.39 - 5.61)		2.21	(1.00 - 4.84)		2.29	(1.05 - 5.01)	

* Exclude 9 women who underwent induction of labor from the analysis.

† Mean and median was obtained from data of women who received oxytocin for augmentation of labor (Case n=62, Control n=42).

‡ Logistic regression model 1(simultaneous method) :Odds ratio adjusted for parity, uterine atony, episiotomy, perineal tear, vaginal laceration, birth weight and birth height.

§ Logistic regression model 2 (Backward stepwise selection method): Variable not in the final model: parity, no perineal tear or 1st degree.

‖ Cutoff points correspond to the 75th percentiles of their distribution in the control group rounded to the approximation value.

Table 3.8. Summary of variables associated with postpartum hemorrhage, arranged in descending order of the odds ratio *

	Adjusted OR †	95% CI	*p*
Uterine atony	31.61	(3.88 - 257.27)	0.001
Perineal tear ≥ 2nd degree	5.12	(1.40 - 19.16)	0.015
Vaginal laceration	3.26	(1.22 - 8.75)	0.019
Episiotomy	1.95	(1.29 - 2.94)	0.001
Low birth weight	0.27	(0.10 - 0.74)	0.11
Multipara ≥ 4	0.12	(0.02 - 0.79)	0.27

* Exclude 9 women who underwent induction of labor from the multivariate analysis.

† Backward stepwise selection method

4. Discussion

4.1. Risk factors for postpartum hemorrhage

The present case-control study was carried out in the National Maternity Hospital in San Salvador, El Salvador, to identify the risk factors for PPH, while focusing on the association between the level of oxytocin exposure and the risk of PPH.

Our results indicate that labor augmentation was not associated with the increased risk of PPH (adjusted OR: 1.50, 95% CI: 0.91–2.46) in El Salvador. However, this finding is different from that of previous studies, which have reported ORs ranging from 1.4 (Israel) to 2.2 (the UK) [14-16, 18], although our finding was similar to that of a Sosa et al.'s study in Argentina and Uruguay (Latin America), which reported that the administration of oxytocin during labor was not associated with PPH [79]. However, Sosa et al. also indicated that one of the limitations of their study was the lack of information regarding the oxytocin infusion duration, which may have affected their findings. In addition, these previous studies did not attempt to quantify the amount of oxytocin that was administered, while our study specifically quantified the levels of oxytocin exposure. Until now, only a few studies have attempted to quantify oxytocin exposure, although we have compared our quantified oxytocin exposures (total dose, maximal rate, duration of infusion, and time at the maximal rate) to the exposures reported in case-control studies that were conducted in France, the USA, and Sweden (Table 4.1) [58, 80, 81]. Subsequent analysis revealed that the mean maximal rate of infusion is higher in El Salvador compared to the rates in France and the USA, although the mean values for the remaining three items were similar between the various countries. For example, the mean maximal rate for our cases and controls was 12.0

mIU/min and 11.0 mIU/min, respectively, compared maximal rates of 9.8 mIU/min and 8.2 mIU/min, respectively, in the French study, and 11.6 mIU/min and 7.0 mIU/min, respectively, in the American study [58, 80].

I In our results, a significant linear trend was observed in the duration of oxytocin infusion ($p = 0.090$), and the time at the maximal infusion rate ($p = 0.048$) (Table 3.7). However, when each category of oxytocin exposure and the risk of PPH were compared, there was insufficient evidence to indicate a clear association between the categorized oxytocin exposure and the risk of PPH. In short, our results do not support the study's hypothesis that higher exposure levels of oxytocin administration might increase the risk of PPH, except for the findings regarding the higher level of exposure in time at the maximal infusion rate. Those findings may be explained by differences in each individual's oxytocin receptor sensitivity (in the uterine muscle) affecting our results. For example, among women who are highly responsive, oxytocin is effective at a low infusion rate, while a higher infusion rate is needed for women who are less responsive to oxytocin.

According to the previous literature, the correlation between the oxytocin infusion rate and the natural levels produced during labor has been reported, with an infusion rate of 4–6 mIU/min providing serum levels that correspond to the levels of oxytocin that are spontaneously produced during the first stage of labor [82]. However, the upper limit for the maximal infusion rate is set at 20 mIU/min in El Salvador, versus the 60 mIU/min limit proposed by the WHO [31], and these levels are approximately 4-fold and 12-fold, respectively, higher than the normal physiologic oxytocin levels produced during

spontaneous labor. Therefore, healthcare providers should be aware that these upper limits are extremely high for women whose oxytocin receptors have high sensitivity.

In this study, we did not observe a significant association between the augmentation of labor and PPH, nor did we observe a clear dose-response relationship with oxytocin use. There are four possible explanations for these results. The first explanation is that there was little difference in the oxytocin exposures of our case and control groups, which is in contrast to the large difference observed between the exposure of the American cases and controls (Table 4.1) [80]. For example, the mean total oxytocin dose for our cases and controls was 2.8 IU and 2.0 IU, respectively, compared doses of 10.0 IU and 3.8 IU, respectively, in the American study. The second explanation may be that a smaller proportion of our subjects received oxytocin for induction or augmentation of labor. For example, 24.1% of our cases and 16.2% of our controls received oxytocin during the first and second stages of labor, compared to 73% of cases and 61% of controls in the French study [58]. The third explanation may be that the definition of PPH affected our results, because we evaluated the association between the augmentation of labor and the risk of PPH (blood loss of $\geq$ 500 g). In contrast, previous studies that evaluated the induction or augmentation of labor as a risk factor for PPH had defined PPH as blood loss of more than 1,000 – 1,500 mL [14, 16 - 18, 58, 80]. The fourth, and most important explanation, may be that the routine use of prophylactic oxytocin during AMTSL may protect against PPH, thereby creating ambiguous study results, which may explain why only the high level of exposure in the time at the maximal infusion rate was significantly associated with the risk of PPH. However, our results were similar to those of the French study [58], which reported that the association between oxytocin use (for

labor augmentation) and the risk of PPH was significant only for the highest category of exposure among the women who received prophylactic oxytocin during the third stage of labor, even though a clear dose-response relationship was observed among the women who did not receive prophylactic oxytocin in the French study. Moreover, our results imply that oxytocin administration is managed relatively well at the National Maternity Hospital during the early stages of labor.

In association with the protective role of oxytocin against PPH, the possibility of a reverse causal relationship between oxytocin administration for labor augmentation and the risk of PPH should be discussed. Based on our exclusion criteria, individuals with antenatal hemorrhage or hematological disorder were excluded from the study, thereby ensuring that all women whose labor was augmented receiving oxytocin prior to postpartum bleeding in this setting. Therefore, this temporal sequence may preclude the possibility of an effect-cause relationship. Furthermore, the author's direct observation of the physicians at the National Maternity Hospital revealed that they were more likely to use oxytocin to prevent fetal distress and infection resulting from the prolonged labor, rather than to prevent PPH.

We believe that our results may indicate the reason for the high prevalence of PPH in El Salvador (30.3%) compared to the global prevalence of PPH (6.1%). Although 100% of the women who have delivered in El Salvador's public hospitals have received prophylactic oxytocin, our results indicate that severe perineal tears, vaginal laceration, and episiotomy were important risk factors that were significantly associated with the increased risk of PPH (approximately 5-fold, 3-fold, and 2-fold, respectively). Uterine

atony was also significantly associated with PPH, with an adjusted OR of 30.91, although, uterine atony was not risk factor of PPH, but rather a cause of PPH, as described in Table 1.1. In addition, the classification of the causes of PPH revealed that traumatic bleeding was responsible for 76.0% of the PPH cases, whereas atonic bleeding was observed in 2.3% of the cases, and a combination of uterine atony and genital tract trauma was observed in 8.7% of the cases. These results are unique, as our data are markedly different from those of a previous study, which indicated that uterine atony and traumatic bleeding was responsible for 70% and 20% of PPH cases, respectively [9]. In addition, it is important to note the association between oxytocin use during the early stages of labor and the frequency of perineal and vaginal laceration. Previous studies have reported that higher doses of oxytocin decrease the time to delivery, compared to the time for lower dose regimens [82-84], and other studies have reported an association between severe perineal tears and labor induction and augmentation, as well as episiotomy [48-51]. After evaluating the results of our study and the previous studies, it appears that an excessive dose of oxytocin may excessively shorten the delivery time, thereby leading to cervical, vaginal, and perineal laceration, due to the rapid decent of the fetal head before the birth canal has sufficiently softened. As shown in Table 4.1, a comparison of the previous studies reveals that the mean maximal rate of oxytocin infusion is higher in El Salvador, compared to the rates in France and the USA. Therefore, the frequent perineal and vaginal tears in our case group may be explained by the high rate of oxytocin infusion in our study. In contrast, a lower dose was associated with a prolonged duration of oxytocin infusion. It has been reported that oxytocin-induced desensitization appears to occur at approximately 4.2 h, therefore prolonged oxytocin infusion may induce uterine fatigue, followed by uterine

atony [85]. However, El Salvador's MoH and the WHO have not set a limit for the duration of infusion, and it is decided by the attending physician. While this study did not demonstrate a clear dose-response relationship between oxytocin administration during the first and second stages of labor and the risk of PPH, oxytocin-containing infusions should be administered while careful monitoring the mother and fetus to maximize patient safety and therapeutic benefit. Moreover, the healthcare provider should be adequately educated regarding the risks associated with labor induction and augmentation.

Considering the low percentage of uterine atony (2.3%) among the 236 women with PPH, our results suggest that AMTSL contributed to the reduced atonic bleeding. However, AMTSL neither prevents nor controls traumatic bleeding, as only the suturing of a wound can stop bleeding from the tears, and laceration is likely associated with overdose administration of oxytocin for labor induction and augmentation. Therefore, oxytocin should be carefully utilized during the first and second stages of labor, and excessive doses of oxytocin for labor induction and augmentation should be avoided. In addition, the use of unnecessary or early episiotomies should also be minimized. Based on our findings, El Salvador's MoH should consider improving the quality of obstetric and midwifery care during the first and second stages of labor, as this is an essential step in reducing the prevalence of PPH.

4.2. Study limitations

The findings of this study should be interpreted carefully, due to the following limitations. First, there may be limitations regarding the generalizability of the study

results, as this study was conducted in single tertiary national hospital that is located in an urban area of El Salvador's capital city. In El Salvador, only 29 public hospitals provide medical services for delivery, and these hospitals also function as teaching hospitals for medical and nursing students. However, the proportion of caesarean section deliveries was approximately 40% at the study hospital, compared to the national average of approximately 30% [70]. Therefore, the National Maternity Hospital, as the sole tertiary hospital in El Salvador, may treat a greater proportion of women with severe complications. Furthermore, this hospital is the only training center for obstetrics medical residents, who have limited firsthand experience with birth assistance, which may also contribute to the higher prevalence of PPH (30.3%) compared to the national prevalence in El Salvador. Moreover, 96% of the births were assisted by skilled birth attendants, such as physicians and nurses, and 85% of the births in El Salvador are facility-based [70]. However, data was not available regarding the 15% of women who did not select the free public childbirth services. Therefore, it is possible that these 15% of women (minus those who utilized private clinics) may have a higher risk of PPH compared to women who had deliveries in the public hospitals.

Second, the results of this study may contain bias. For example, although caesarean deliveries are an important risk factor for PPH [14, 15, 17, 18, 20-22], they were excluded from this study due to the logistical challenges regarding blood loss data collection. In addition, women who underwent labor induction were also excluded, as only two women who received oxytocin for labor induction were identified during the study period. Furthermore, the rate of labor induction and augmentation at the National Maternity Hospital (21.5%) was lower than the rates in Egypt (91%) (86), Southern

American countries (61%) [22], and Jordan (42%) [87], where elective inductions are routinely performed for convenience or at the patient's request. Several factors may have contributed to our relatively low rate of labor induction, including (i) very few women actually received oxytocin for labor induction, (ii) hospital staff did not actively approach women who were undergoing labor induction to participate in the study, and (iii) the number of women experienced failed labor induction and subsequently underwent caesarean deliveries. In fact, previous studies have reported that failed labor induction was related to the risk of PPH [88, 89]. Regrettably, information regarding the medical indications for caesarean section was not available, and we did not collect data regarding failed labor induction or augmentation. Therefore, only women whose labor induction or augmentation was successful were involved in this study. Moreover, it is pertinent to consider the relatively low coverage (65%) of the study participants, as 870 patients among 1,333 eligible women participated in the study despite the day-to-day supervision by the research team. If the study had achieved a higher participation rate, this might have affected our findings.

Although our study has the various limitations that are mentioned above, we believe that our findings provide important insight regarding the risk factors for PPH, and that they will contribute to reducing the prevalence of PPH in El Salvador. However, to increase the representativeness of the study population and the generalizability of the study results, a multicenter study in a broader and more diverse population will be needed, ideally one that involves all 29 public hospitals that provide delivery services in El Salvador.

In addition, when our prevalences of PPH (30.3%) and SPPH (4.0%) are compared to the official prevalences of PPH (1.7%) and SPPH (0.6%) at this hospital, it appears that the prevalences of PPH and SPPH have been extremely underestimated in El Salvador. Furthermore, considering the global prevalences of PPH (6.1%) and SPPH (1.86%), which were obtained via systematic reviews of 120 datasets and 70 datasets, respectively [26], it appears that the global prevalences of PPH and SPPH might also be underestimated. To understand the true global prevalence of PPH, further studies in other developing countries are urgently needed.

Table 4.1. Comparison of mean and median oxytocin exposure between El Salvador and other developed countries

Country (Year)	Outcome	Sample size		Measure	Total dose (IU)		Maximal rate (mIU/min)		Duration (min)		Time at the maximal rate (min)	
					Case	Control	Case	Control	Case	Control	Case	Control
El Salvador (This study) (2014)	Postpartum hemorrhage	Case: Control:	263 263	Mean	2.8	2.0	12.0	11.0	308	229	145	100
				Median	2.1	1.5	10.0	10.0	267	193	118	64
France (2011)	Severe postpartum hemorrhage	Case: Control:	1,483 1,758	Mean	2.4	1.6	9.8	8.2	295	217	128	103
				Median	1.6	0.9	8.3	7.5	266	182	100	78
USA (2011)	Severe postpartum hemorrhage	Case: Control:	54 54	Mean	10.0	3.8	11.6	7.0	684	330	n/d	n/d
Sweden (2012)	Retained placenta	Case: Control:	408 408	Median	n/d	n/d	n/d	n/d	270	150	n/d	n/d

5. Conclusions and recommendations

As described in the title of this thesis, the purpose of the present study was to assess the association between the level of oxytocin exposure during the first and second stages of labor and the risk of PPH. The results indicate that labor augmentation was not a risk factor for PPH among Salvadoran women, and there was insufficient evidence to indicate a clear dose-response relationship between the categorized oxytocin exposure and the risk of PPH. However, this study revealed that several factors were related each other and contributed to the elevated risk of PPH; traumatic bleeding was identified as an important causative factor. As traumatic bleeding could be the consequence of oxytocin use during the first and second stages of labor, further detailed analysis regarding this issue is necessary. Given the fact that traumatic bleeding was responsible for 76.0% of Salvadoran PPH cases, and El Salvador has an extremely high prevalence of PPH (30.3% vs. 6.1% globally), the current standard strategy of preventing PPH by focusing on the third stage of labor (AMTSL), with little regard for the first and second stages of labor, appears to be somewhat futile in reducing the prevalence of PPH. Although AMTSL seems to have effectively reduced the risk of uterine atony to a certain extent, as only 2.3% of Salvadoran women were complicated with PPH in this context, the effect of AMTSL on the risk of PPH is not well understood. Therefore, it is recommended that further studies should be conducted, and that healthcare personnel should be educated regarding the known risks of PPH, as well as the risks related to labor induction and augmentation.

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8. Appendices

Appendix 1: Preliminary study 1

Comparison of blood loss after vaginal deliveries as evaluated using visual estimation and direct measurement at the National Maternity Hospital in El Salvador

エルサルバドル国立産科病院における産後出血量の目測値と実測値の比較

1. Introduction

Post-partum hemorrhage (PPH) is a major cause of maternal mortality and morbidity, particularly in developing countries [1]. Maternal mortality and morbidity resulting from PPH depend mainly on the accurate estimation and management of postpartum blood loss, because the delayed detection of PPH may lead to increased mortality and morbidity [2,3]. However, measurement of postpartum blood loss with accuracy remains a major problem in international literature.

The current standard practice of postpartum blood loss assessment in developing countries is visual estimation. Multiple studies published since the 1960s have shown that visual estimation is an un- reliable and may be underestimated by as much as 30% to 90% of actual value for blood loss [4-11]. To improve the performance of PPH detection more accurately, other definitions were proposed, such as a peripartum change in hematocrit of > 10% or decrease in hemoglobin of > 4g/dl [12,13]. Nonetheless,

those definitions may not practical because hematological test results cannot reflect to the acute change of blood loss of patients, and laboratory equipment and human resources are not always available to examine, especially in rural area of developing countries.

In El Salvador, amount of postpartum blood loss was estimated visually. Postpartum hemoglobin and hematocrit values were not routinely obtained, although admission hemoglobin and hematocrit values were routinely analyzed. In this context, detection of case with PPH was difficult, and it is needed to introduce an alternative method to detect PPH systematically in El Salvador. One candidate to improve the diagnostic performance of PPH is direct measurement, which was one of the most traditional methods and was proven to be more accurate [14].

The study was conducted as part of training in an attempt to the introduction of blood loss measurement as routine practice in the National Maternity Hospital. This study aimed to compare the amount of blood loss evaluated between visual estimation and direct measurement in women who delivered vaginally in order to assess the diagnostic performance of both methods in detecting primary PPH.

2. Methodology

2.1. Study design

A comparison of amount of bleeding after vaginal delivery evaluated by visual estimation and by direct measurement was made. This study was carried out as a preliminary study 1 of the study entitled "Does oxytocin administration during the first and second stages of labor increase the risk of postpartum hemorrhage? A case-control study at the National Maternity Hospital in El Salvador", during the period from 1st April and 30 June 2014, simultaneously with the preliminary study 2.

The inclusion criteria were consented women to the study participation who had vaginal delivery during the study period, with gestational age of 35 weeks or more. Women with mild complications, multiple pregnancies (> 2 fetuses), patients admitted with complete cervical dilation were also included. The exclusion criteria were women delivered by caesarean section, intrauterine fetal death, presence of antenatal hemorrhage, and patients with severe complications.

2.2. Data collection procedure

The procedures of data collection are summarized in following three steps.

Step1: Postpartum blood loss was collected during the third stage of labor and during the postpartum medical procedure by attending doctors.

Step 2: Once the postpartum medical procedure was completed, attending doctors and nurses estimated the amount of postpartum blood loss independently by visual means. It

takes up to 5 minutes to complete direct measurement.

Step 3: Immediately after the visual estimation of blood loss, amount of bleeding was measured objectively using measuring cup and scale by attending doctors and nurses.

Hereafter, detailed data collection procedures are described. All eligible women were approached when they were admitted to the labor room. After obtained women's agreement to participate in the study, women were closely monitored and provided obstetric services as routine practices in the labor room.

Once full cervical dilatation was confirmed, women entered to the delivery room and lay on the delivery bed. To collect blood loss, two basins and two sterilized sheets were used in delivery room. The attending doctor set the first basin under the delivery bed (Photo 1), and disinfected the genital area using sterilized water. Later, the first sterilized sheet was placed under the buttocks of the women. When baby was born and clamped and cut the umbilical cord, the first sheet and the first basin contaminated by the gush of amniotic fluid, sterilized water, blood from the laceration of episiotomy, urine and feces were immediately removed, and another (second) sheet and basin were newly replaced to collect purely postpartum bleeding. The removed sheet and basin were not included in the measurement.

Normally, the third stage of labor is referred to as the time from the birth of the baby to the expulsion of the placenta and membranes. However, it is needed to clarify that in this study, the third stage of labor was defined as the period from just after the delivery

of the baby to completeness of medical procedure at the delivery room. This period contains clamping and cutting of the umbilical cord, expulsion of the placenta, suture of genital tract trauma, inspection and cleanliness of genital area. During this period, women spent on the delivery bed. Length of time of this period varied from 10 minute to more than 1 hour.

Once the patient was ready to be transferred to the recovery room from the delivery room, both the attending doctor and attending nurse estimated postpartum blood loss by visual means.

After that, the weight of all the collected gauzes and sheet, blood pooled in the basin and container of placenta was measured by scale and plastic graduated cup (Photo 2-4). Out of the total weight obtained, the dry weight of the gauze and sheet was subtracted. Then, weight represented the actual blood loss during the third stage of labor was obtained by direct measurement. The blood in the plastic graduated cup was converted 1 milliliter (ml) into 1 gram (g).

2.3. Data analysis

To verify the accuracy of the blood loss estimation in the third stage of labor, a graph was drawn illustrating the simple linear regression results at a significance level of 5%. Tables and figures were prepared using Microsoft Excel spreadsheets (Microsoft Corp., Redmond, WA, USA). Statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (IBM/SPSS Corp., Chicago, IL, USA).

3. Results

3.1. Comparison of PPH detection rate between visual estimation and direct measurement

Amount of postpartum bleeding evaluated by visual estimation and by direct measurement was compared, and the professional differences to detect PPH were assessed. Among 870 women whose blood loss was directly measured, 727 (83.6%) women were visually estimated by doctors, and 672 (77.2%) women were visually estimated by nurses. In total, 650 (74.7%) women had complete three sets of data: visual estimation by doctor, visual estimation by nurse, and direct measurement. For comparison, data of those 650 women was utilized.

Table 1 showed the mean visually estimated blood loss by doctors was 290g (SD ± 198.5), mean estimated blood loss by nurses was 282g (SD ± 197.4), while the mean measured blood loss was 337g (SD ± 262.9).Visual estimation of doctors and nurses underestimated postpartum blood loss by 13.9% and 16.3% compared with the direct measurement, respectively. Table 2 and Table 3 demonstrated the accuracy of the blood loss estimation in the third stage of labor by doctors and by nurses, respectively. Visually estimated blood loss by doctors had 45.9% sensitivity, 91.1% specificity and 83.4% accuracy in detecting PPH using direct measurement as a gold standard. Once again, visually estimated blood loss by nurses had 43.2% sensitivity, 94.4% specificity and 85.7% accuracy in judging whether PPH or not.

3.2. Correlation between the visually estimated blood loss and the measured blood loss

To validate the visually estimated blood loss during the third stage of labor, correlation between estimated and measured blood loss were compared by profession. Dataset of 727 (83.6%) women was used for analysis of doctors' performance, and dataset of 672 (77.2%) women was used for analysis of nurses' performance. The change of the correlation was observed monthly.

In the Figure 1 and 2, estimated blood loss was plotted. Analysis of simple linear regression showed a gradual improvement of correlation (R^2) between the estimated blood loss by doctors and the measured blood loss from 0.394 in the first month to 0.593 in the third month (Figure 1), while overall correlation during the study period of three months was 0.478 ($p < 0.001$). Besides, association between the estimated blood loss by nurses and the measured blood loss showed little change of correlation (R^2) between the first month (0.502) and the third month (0.520), although no correlation was found in May (0.381) (Figure 2). Overall correlation during the study period of visual estimation by nurses was 0.475 ($p < 0.001$).

Figure 3 showed the plotting the difference between blood loss estimated by doctors and measured blood loss against measured blood loss, and there was moderate correlation (R^2=0.502). Figure 4 also showed the difference between blood loss estimated by nurses and measured blood loss against measured blood loss (R^2=0.450). Although there was little correlation, both figure explained the trend of underestimation in large bleeding.

4. Discussion

While visual estimation is the most frequent method used to determine blood loss in developing countries, this study demonstrated the inaccuracy of visual estimation when compared to blood loss measured by direct measurement.

A linear correlation showed the significant difference between the visually estimated blood loss and the gravimetric calculation of blood loss by doctors and nurses ($P < 0.001$). However, it is worth noting that the diagnostic performance of attending doctors was gradually improved month by month, while the change of the diagnostic performance was not seen among nurses. This may be explained by the fact that attending doctors could observe whole process of bleeding at the beginning of the second stage of labor until complete the postpartum medical procedure, whereas it was impossible for nurses because they were responsible for at least 3 or 5 parturient women in progress of labor or in postpartum period.

When blood loss evaluated by direct measurement was regard to gold standard, the sensitivity of visual estimation both by doctors and nurses was less than 50%. More than half of women who were complicated with PPH were not detected by visual estimation. Comparison of mean blood loss between visual estimation by doctors and nurse underestimated 13% and 16% less than that evaluated by direct measurement. While those values were relatively well than degree of underestimation reported in the previous studies of 30% to 90%, and difference of such 13% and 16% in our study may not be clinically meaningful in women sustaining a small blood loss (mean difference of 47g and 55g, respectively). However, with a greater blood loss the 13% or 16% of

underestimation of visual estimation may well have a significant impact on maternal survival. For example, visually estimated blood loss by an attending doctor was 800g against the real bleeding of 1852g measured directly. The difference between estimated and measured blood loss was -1052g. It means that doctor underestimated -1052g of bleeding, and this value was not small concern.

Considering the fact that the official prevalence of PPH was 1.7% in the National Maternity Hospital in 2013, the detection of 15.2% of PPH by doctors and 12.0% of PPH by nurses seemed to be somewhat good result rather than before.

In summary, it is recommended that attending doctors continue direct measurement of blood loss in order to identify the more women who are suffering from PPH, and provide appropriate treatment for PPH immediately after its detection.

5. Photos, tables and figures

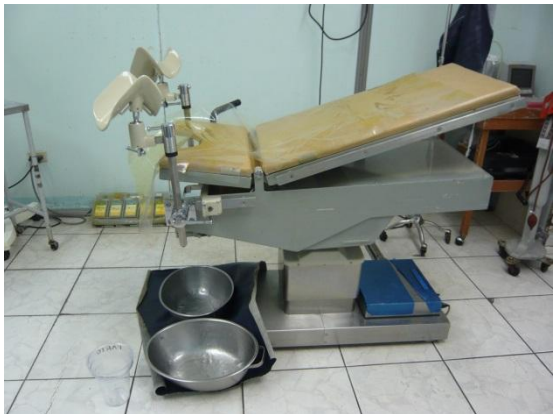


Photo 1.
Two basins and plastic graduated cup were set under the delivery bed.

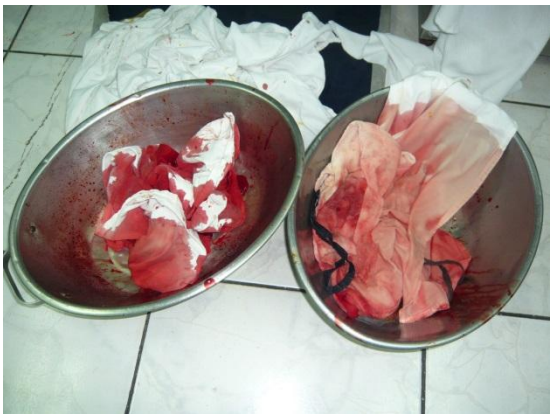


Photo 2.
The basin and sheet on the left were used during the third stage of labor, and those on the right were used during the second stage of labor.

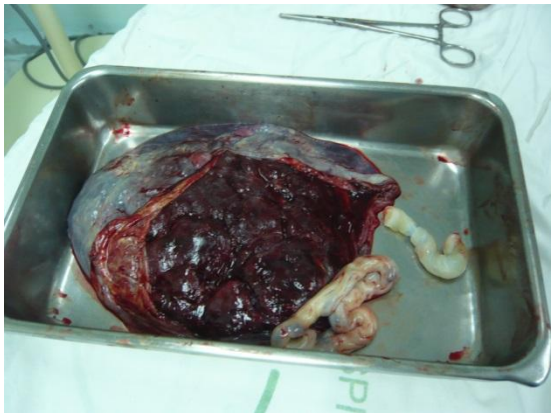


Photo 3.
Blood collected in the container of placenta and coagula inside the placenta membrane were measured by using scale or plastic graduated cup.

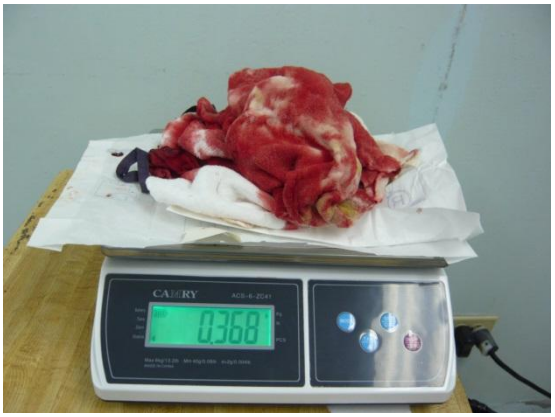


Photo 4.
Blood soaked into the sterilized sheet and gauzes were measured by scale.

Table 1. Comparison of the mean blood loss by different evaluation methods between visual estimation and direct measurement

	Visual estimation by doctors	Visual estimation by nurses	Direct measurement
	n = 650	n = 650	n = 650
Mean ± SD	290 198.5	282 197.4	337 262.9
(Range) (g)	(10 - 2,000)	(0 - 1,700)	(0 - 2,170)

Table 2. Diagnostic performance of visual estimation by doctors in the detection of postpartum hemorrhage

Visually estimated postpartum hemorrhage by doctors	Postpartum hemorrhage by direct measurement		
	Blood loss ≥500g	Blood loss <500g	Total
Blood loss ≥500g	51	48	99
Blood loss <500g	60	491	551
Total	111	539	650

*Sensitivity = 51/111 = 45.9%; Specificity = 491/539 = 91.1%; Positive predictive value = 51/99 = 51.5%; Negative predictive value = 491/551 = 89.1%; Accurecy = (51+491)/650 = 83.4%

Table 3. Diagnostic performance of visual estimation by nurses in the detection of postpartum hemorrhage

Visually estimated postpartum hemorrhage by nurses	Postpartum hemorrhage by direct measurement		
	Blood loss ≥500g	Blood loss <500g	Total
Blood loss ≥500g	48	30	78
Blood loss <500g	63	509	572
Total	111	539	650

* Sensitivity = 48/111 = 43.2%; Specificity = 509/539 = 94.4%; Positive predictive value =48/78 = 61.4%; Negative predictive value =509/572 = 89.0%; Accurecy = (48+509)/650 = 85.7%

Figure 1. Association between visually estimated blood loss by doctors and measured blood loss by month.

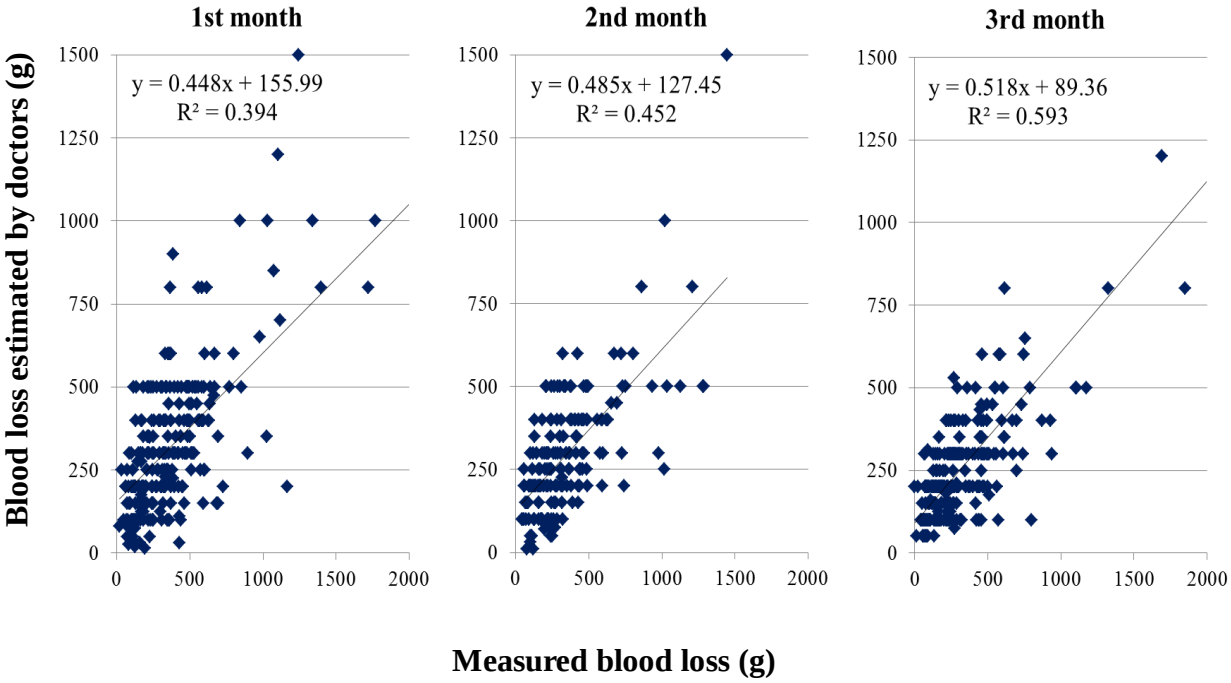


Figure 2. Association between visually estimated blood loss by nurses and measured blood loss by month.

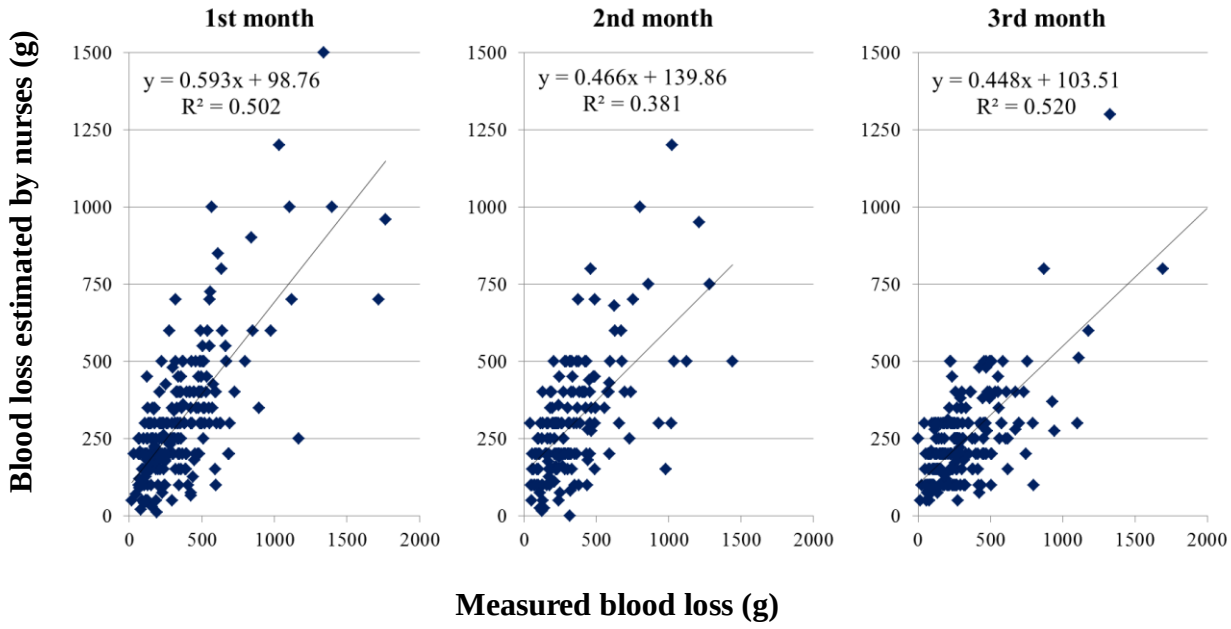


Figure 3. Association between difference of estimated blood loss by doctors and measured blood loss and measured

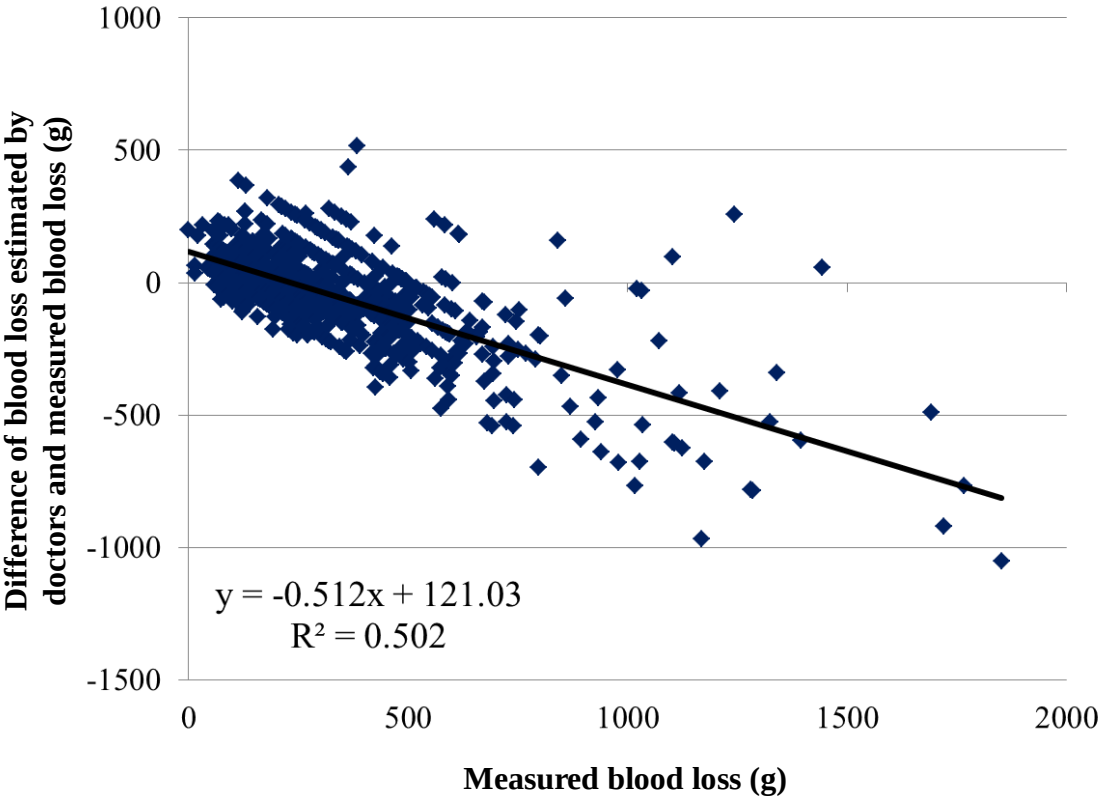
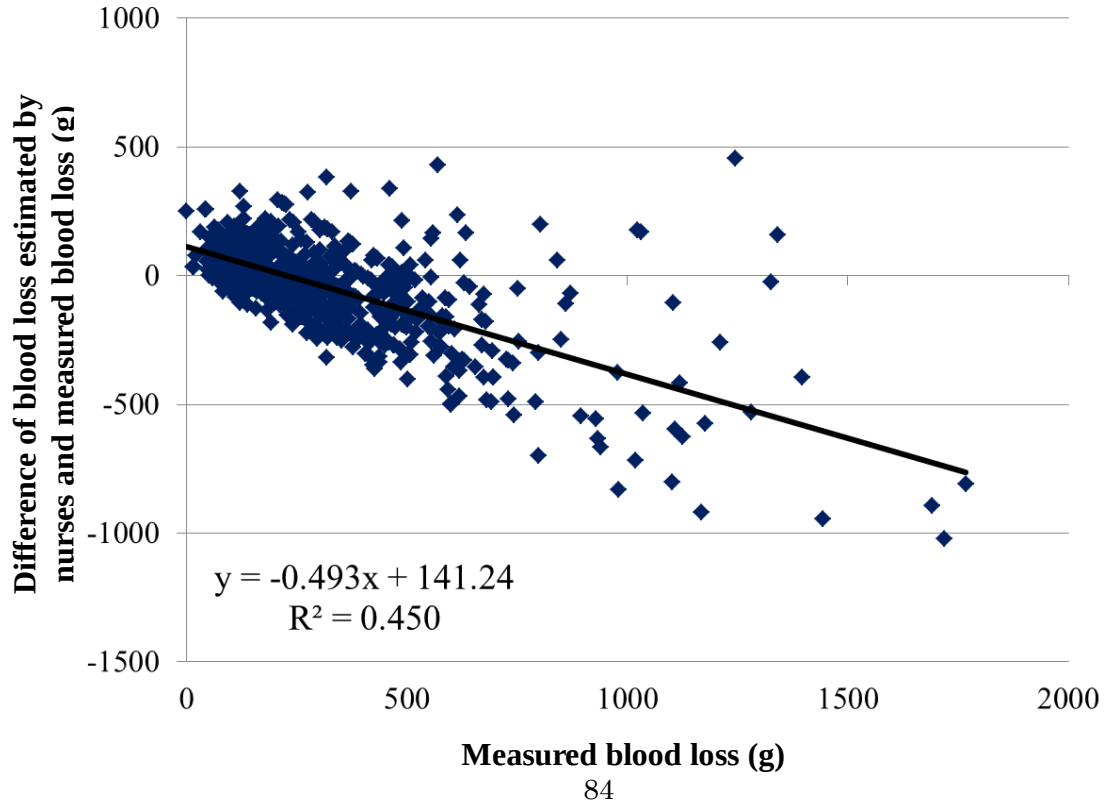


Figure 4. Association between difference of estimated blood loss by nurses and measured blood loss and measured



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Appendix 2: Preliminary study 2

The prevalence of postpartum hemorrhage after virginal delivery at the National Maternity Hospital in El Salvador

エルサルバドル国立産科病院における経膣分娩後の産後多出血有病率

1. Introduction

The official data of the National Maternity Hospital of El Salvador in 2013 indicated that prevalence of postpartum hemorrhage (PPH) was 1.7% and severe postpartum hemorrhage (SPPH) was 0.6%. The prevalence in El Salvador was lower than the global prevalence of PPH (6.1%) obtained from systematic review of 120 dataset related to PPH [1]. Note that in El Salvador, postpartum blood loss was evaluated by visual estimation which seemed to be inaccurate being up to 90% less than actual value for blood loss [2]. Besides, there were 17 maternal deaths in this hospital in 2013, including at least four (23.5%) maternal deaths due to PPH. This number of maternal deaths due to PPH was too important to overlook while prevalence of PPH in this hospital was considerably low. Women who were complicated with PPH seemed to be less likely to be detected in El Salvador.

This study aims to determine the prevalence of PPH and SPPH after vaginal deliveries in the National Maternity Hospital of El Salvador.

2. Methodology

2.1. Study design

A cross-sectional design was chosen to identify the women with PPH and SPPH after vaginal delivery at the National Maternity Hospital in El Salvador, from 1st April until 30 June 2014, simultaneously with the preliminary study 1.

The Inclusion and exclusion criteria of study participants were as same as preliminary study 1.

2.2. Study variables

The main outcome measure was postpartum blood loss. PPH and SPPH were defined as blood loss of ≥ 500g and ≥ 1,000g after vaginal delivery, respectively. Blood loss collections began immediately after delivery of baby, and continued for a maximum of 4 hours after delivery.

3. Results

During the study period, there were 2,684 deliveries, consisted of 1,591 (59.3%) vaginal deliveries and 1,095 (40.7%) caesarean sections. Of 1,591 vaginal deliveries, the following 258 women were excluded from this population: 134 whose gestational age had not progressed to 35 weeks, 105 who had severe obstetric complications (severe pre-eclampsia, severe gestational diabetes, and severe cardiac disease), 17 who had intrauterine fetal death (IUFD), and 2 who required medical treatment under anesthesia after vaginal delivery (one for severe placenta accrete and the other for hematoma), and the remaining 1,333 women were met the inclusion criteria for the study. Of 1,333 target women, 870 (65.3%) participated in the study. During the same time period, there were four maternal deaths due to intracerebral hemorrhage, chorioamnionitis, sepsis and shock during labor. Out of 4, one death was included in the cross-sectional study and she did not have PPH.

Among the 870 women, PPH was identified in 264 (30.3%) women, and SPPH were identified in 43 (4.9%), including 4 (0.5%) women having blood loss more than 2,000g. Median of total blood loss was 374g, and the range of bleeding was from 0 to 2,637g. Figure 1 shows the distribution of the total blood loss divided into 100g units. The group of blood loss from 300-399g was most frequent (20.9%), and group of 200-299g was the next (19.8%).

4. Discussion

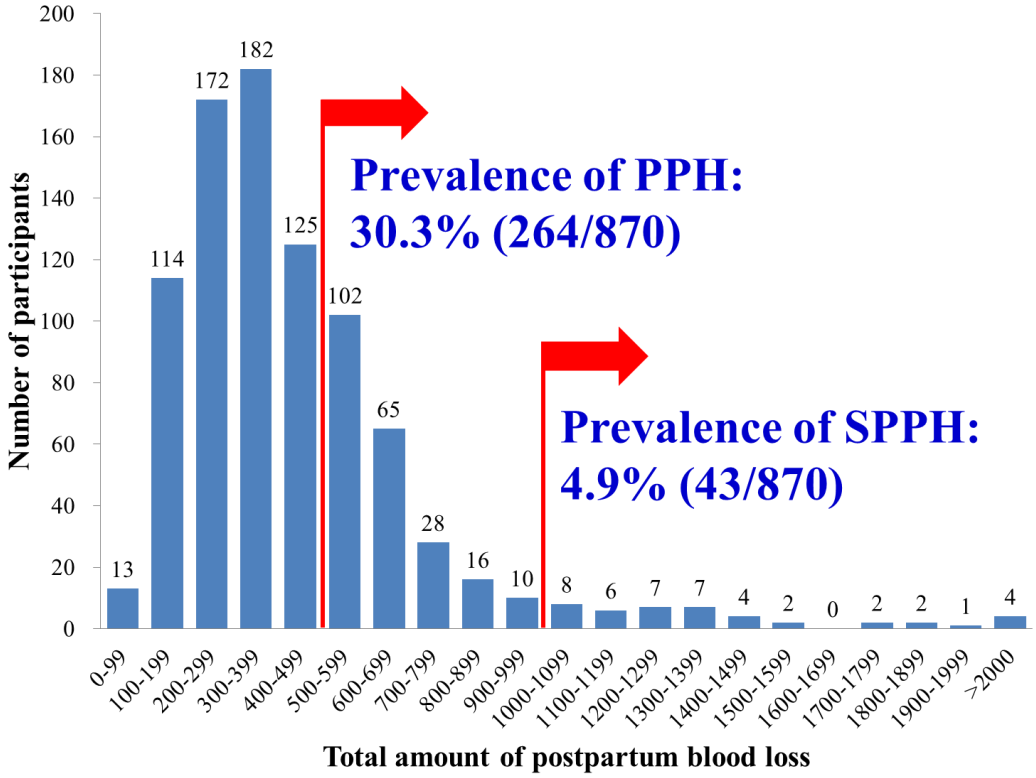
This study was the first study to determine prevalence of PPH utilized data of objectively measured postpartum blood loss in El Salvador. Present study indicated that PPH and SPPH in the national maternal hospital in El Salvador was 30.3% and 4.0%, respectively. Compared to the official prevalence of PPH (1.7%) and SPPH (0.6%) in this hospital in 2013, the study result had about 18 times higher prevalence of PPH, and 8 times higher prevalence of SPPH. This study result was also higher than the SPPH of previous study carried out in El Salvador was 1.49% [3]. This study revealed that prevalence of PPH had been heavily underestimated in El Salvador.

To assess the accuracy of the health information system of the hospital, the prevalence of PPH and SPPH in this study were compared with those of official data obtained from the health information system of the hospital over the same time period from 1st, April to 30, June in 2014. The prevalence of PPH in this study was 30.3% (=264/879) whereas 1.7% (=27/1,591) in the official data of the hospital. Once again, the prevalence of SPPH in this study was 4.0% (43/870) whereas 0% in the official data (=0/1,591). This comparison demonstrated that the National Maternal Hospital had failure in documentation system.

In short, this study highlighted two fundamental problems that (i) PPH was not adequately detected, and (ii) PPH was not correctly registered with the information system.

5. Figure

Figure 1. Distribution of amount of postpartum blood loss



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Appendix 3: Approval from the Research Ethics Committee of Graduate School of Medicine of the University of Tokyo

倫　理　委　員　会
審 査 結 果 報 告 書

平成26年01月27日

申請者（研究責任者）
生物医化学
教授
北 潔　殿

東京大学大学院医学系研究科長・医学部長
宮園　浩平

審査番号　10372

研究課題　エルサルバドル国における陣痛誘発・促進を経験した女性の産後多出血に関わるリスク因子の探索を目的とした症例対照研究（多施設共同研究）

上記研究計画を平成26年01月20日の委員会で審査し下記のとおり判定しました。
ここに通知します。

判　定

○承認する	条件付きで承認する
変更を勧告する	承認しない
該当しない	

Appendix 4: Approval from the Research Committee for Health Research of the National Maternity Hospital of El Salvador

ANALISIS METODOLOGICO PARA PROTOCOLOS DE INVESTIGACIONES OBSERVACIONALES

I.- Solicitud de autorización para realización de investigación clínica

Titulo de la investigación	Hemorragia postparto
Investigador principal	Dra. Emi Sasagawa
Co-investigadores	
Tipo de investigación	Retrospectiva-longitudinal
Fecha de entrada del protocolo al comité	9 de Octubre de 2013
Fecha de entrega del protocolo a los miembros del comité	17 de Octubre de 2013
Fecha del dictamen del comité	31 de octubre de 2013

Análisis metodológico	Adecuado	No aplica	Inadecuado
Justificación	X		
Hipótesis	X		
Objetivo general	X		
Objetivos específicos	X		
Tamaño de la muestra	X		
Selección equitativa de sujetos		X	
Pertinencia del instrumento de investigación	X		
Relevancia del tema	X		
Duplicidad del tema	X		
Aceptabilidad técnica	X		
Aplicabilidad de los conocimientos generados	X		
Idoneidad del investigador para el tema (formación experiencia, tiempo suficiente para el estudio)	X		
Mecanismos de resguardo de los datos	X		
Mecanismos de confidencialidad de los datos	X		
Selección equitativa de los sujetos	X		
Idoneidad de sitio de investigación/ instalaciones	X		
Utilidad de la investigación para el hospital	X		
Razón Beneficio/ Riesgo	X		

Declaración de la decisión tomada:

1.- Protocolo aprobado: X
2.- Protocolo rechazado:
3.- Solicitud de enmienda (no se aprueba hasta una modificación completa del protocolo): XXXXX
4.- Protocolo aprobado con recomendación, (alguna recomendación sobre el proceso)

Recomendaciones:

1. Describir mejor la forma de medición directa del sangrado
2. Falta describir que hacer en caso de hemorragia postparto severo en el estudio de casos y controles
3. Aprobado y pasa al Comité de Ética del HNEM

San Salvador 31 de Octubre de 2013

Dr. Efraín Portillo
Comité de Investigacion

Dra. Dalia Xochitl Sandoval López
GINECOLOGIA Y OBSTETRICIA
CIRUGIA ENDOSCOPICA
J.V.P.M. No. 3882

Dra. Xochitl Sandoval
Coordinadora del Comité de Investigacion

Dr. Guillermo Ortiz Avendaño
Comité de Investigacion HNEM

HOSPITAL NACIONAL ESPECIALIZADO DE MATERNIDAD
"Dr. Raúl Argüello Escolán"
COMITE DE INVESTIGACIÓN
San Salvador

Dra. Lizeth Rosa María Elías de Buendía
Comité de Investigacion HNEM

Appendix 5: Approval from the Ethical Committee for Health Research of the National Maternity Hospital of El Salvador

Ministerio de Salud

EL SALVADOR

HOSPITAL NACIONAL ESPECIALIZADO DE MATERNIDAD
"Dr. Raúl Arguello Escolan"
San Salvador

HOSPITAL NACIONAL ESPECIALIZADO
Dr. RAUL ARGUELLO ESCOLAN
COMITÉ DE ETICA DE LA INVESTIGACION.

Ph.D Emi Sasagawa
Facultad de medicina de la universidad de Tokio
Presente

En atención a la solicitud recibida el 1 de Abril del 2014 en con respecto a la revisión y análisis del trabajo de investigación "**ESTUDIOS Y CONTROLES DE LA HEMORRAGIA POST-PARTO, ESPECIALMENTE CON REFERENCIA A INDUCCIÓN Y CONDUCCIÓN DEL PARTO EN EL SALVADOR** "el comité de ética de la investigación (CIEC), amparado en el reglamento interno y normas internacionales, resuelve de conformidad la debida
APROBACION EXPEDITA Para iniciar la investigación pertinente en el trabajo en cuestión.

No omitimos solicitarle el cumplimiento de las observaciones hechas por el comité de investigación del Hospital Nacional Especializado de Maternidad.

Atte.

Hospital Nacional de Maternidad Dr. Raúl Arguello Escolan
PRESIDENTE

Dr. Walter Carranza
presidente

Dra. Ingrid Lizama
Vicepresidenta

Hospital Nacional de Maternidad Dr. Raúl Arguello Escolan
SECRETARIA

Srita. Linda Marianita Cuellar
Secretaria

Appendix 6: Explanatory leaflet for study participants (Spanish)

NOTAS INFORMATIVAS PARA LAS PARTICIPANTES DEL ESTUDIO
Estudio de casos y controles de la hemorragia postparto

Nombre de Investigadora: Emi SASAGAWA
Teléfonos: 7900-6195

Este documento es para explicarle que el Hospital Nacional de Maternidad "Dr. Raúl Arguello Escolán"y la Universidad de Tokio llevarán a cabo un estudio sobre los factores de riesgo de la hemorragia postparto (HPP).

El objetivo del estudio es conocer los factores de riesgo de la HPP, para lo cual se tomaran datos de su expediente durante el trabajo; es decir, durante usted tenga los dolores del parto y permanezca en el hospital en el servicio de partos para el análisis.

La Recolección de los datos se hará después de atención de parto normal y se medirá la pérdida de sangre. No incluye intervenciones invasivas para el estudio.

Su participación es totalmente voluntaria y usted tiene derecho a retirarse de este en cualquier momento o fase del estudio, sin que esto acarree ninguna desventaja o repercusión en su tratamiento.

Sus datos personales e información serán manejados de manera confidencial.

En caso que usted tenga una duda o queja al respecto de este estudio, usted puede comunicarse con la Lic. Emi Sasagawa, miembro de la Investigación al teléfono: 7900-6195

El conocimiento que surgirá del estudio se publicará de manera que la información personal no será identificable.

El estudio estará basado en la observación; por lo tanto, no genera riesgos adicionales. Se le informa además que no se obtendrán beneficios monetarios ni de otro tipo al ser participante del estudio.
Le agredecemos su participación y sabemos que muchas mujeres embarazadas se benefician por la información obtenidas a través del estudio.

Después de finalizar el estudio, la información será guardada por la investigadora durante un período determinado y posteriormente serán destruidas por trituradora.

Appendix 7: Informed consent form (Spanish)

Estudio de casos y controles de la hemorragia postparto,
especialmente con referencia a inducción y conducción del parto en El Salvador

Nombre de Investigadora: Emi SASAGAWA
Teléfonos: 7900-6195

FORMATO DE CONSENTIMIENTO INFORMADO

Me explicó que el Hospital Nacional de Maternidad "Dr. Raúl Arguello Escolán" y la Universidad de Tokio se llevará a cabo el estudio sobre los factores de riesgo de hemorragia postparto (HPP).

El studio fue apropado por el comité ética del Hospital Nacional de Maternidad "Dr. Raúl Arguello Escolán" y de la Posgrado de medicina, Universidad de Tokio.

El objetivo del estudio es conocer la frecuencia de la HPP y entender los factores de riesgo de la HPP. Las informaciones durante el trabajo de parto se colectarán para el análisis.

Estoy de acuerdo de participar en el estudio voluntariamente, y entiendo que el estudio incluye recolección de los datos de mi expediente.

Yo recibí informaciones siguientes y entiendo:

1. Esquema del Estudio
2. Recolección de las Informaciones
3. Participación Voluntaria y el Derecho de Retiro del Estudio
4. Protección de la Información Personal
5. Resultados Compartidos
6. Riesgos y Beneficios
7. Destrucción de la Informción Personal después del Estudio
8. Indemnización
9. Otro

Estoy de acuerdo de participar ☐ No estoy de acuerdo de participar ☐

Nombre y firma de mujer:_____

Nombre de investigador:_____

Fecha: _____ / _____ /2014

Appendix 8: Data collection sheet

1	Nombre de investigador	(1) Dra. Lizeth	(2) Dr. Guillermo	(3) Lic. Navarro	(4) Lic. Barrera	1 name
2	Grupo	(1) Grupo de Casos	(2) Grupo de Controles			2 group
3	Código de estudio	_____				3 code
4	Residencia (departamento)	(1) Ciudad de SAL	(2) Fuera de ciudad Depto. SAL	(3) Otros Depto. _____		4 address
5	Edad	_____ años				5 age
6	Paridad	_____ para				6 parity
7	Cesárea anterior	(1) Sí	(0) No			7 cs
8	Peso al ingreso	_____ kg				8 wt
9	Talla	_____ cm				9 ht
10	Fecha de último período menstrual	Año _____	Mes _____	Día _____		10 lmp
11	Fecha prevista del parto	Año _____	Mes _____	Día _____		11 edd
12	Hemoglobina < 20 semanas	_____ g/dl			N/D (77.7)	12 hbmid
13	Hemoglobina ≥ 20 semanas	_____ g/dl			N/D (77.7)	13 hblate
14	Hemoglobina al ingreso	_____ g/dl			N/D (77.7)	14 hbadmi
15	Hematocrito al ingreso	_____ %			N/D (77)	15 hemato
16	No. consultas prenatales	_____ times				16 anc
17	Estado de transferido	(1) Sí	(0) No			17 transfe
18	Fecha y hora de ingreso	Mes _____	/Día _____	/Hora _____		18 dateadmi
19	Fecha y hora de ruptura de membranas	Mes _____	/Día _____	/Hora _____		19 daterom
20	Edad gestaciaonal	_____ weeks				20 week
21	Fecha y hora de inicio de parto	Mes _____	/Día _____	/Hora _____		21 dateonset
22	Fecha y hora de dilatación cervical completo	Mes _____	/Día _____	/Hora _____		22 datefull
23	Fecha y hora de nacimiento	Mes _____	/Día _____	/Hora _____		23 datebaby
24	Fecha y hora de almbramiento de placenta	Mes _____	/Día _____	/Hora _____		24 dateplace
25	Duración de 1ro período de parto	_____ min (hora min)			N/D (7)	25 latent
26	Duración de fase activa (4cm ~ dilatación completo)	_____ min (hora min)			N/D (7)	26 active
27	Duración de 2nd período de parto	_____ min				27 second
28	Duración de 3ro período de parto	_____ min				28 third
29	Dilatación cervical al ingreso	_____ cm				29 cerviadmi
30	Ruptura de membrane al ingreso	(1) RPM	(0) No ruptura o Saco intacto			30 statusrom
31	Tipo de ruptura	(1) Artificial	(0) Rotura alta & Espontánea		N/D (7)	31 moderom
32	Tipo de parto	(1) Normal	(2) Fórceps	(3) Extracción al vacío		32 modebirth
33	Episiotomía	(1) Sí	(0) No			33 epi
34	Cantidad de sagrado hasta 3ro período de parto	_____ g				34 pphthird
35	Cantidad de sagrado hasta 4to período de parto	_____ g				35 pphfourth
36	Práctica de MATEP	(1) Sí	(0) No			36 amtsl

37	Tipo de inicio de parto	(1) Espontáneo sin conducción	(2) Espontáneo con conducción	(3) Inducción con maduración cervical (Misoprostol)	(4) Inducción con oxitocina		37 modeonset
38	Razón de inducción de parto	**Razón medical:** (1) postérmino > 41 semanas, (2) RPM, (3) FCF Anormal, (4) Oligoamnios, (5) Pre-eclampsia / Eclampsia, (6) Líquido amniótico meconial , (7) Retraso del crecimiento intrauterino (RCIU) sospechoso, (8) Macrosomía sospechosa, (9) Calcificación de placenta, (10) Edema, (11) Proteinuria, (12) Otros **Razón social:** (13) Conveniencia o ninguna indicación específica N/A: (0)					38 reason
39	Fecha y hora de inicio de infusión con oxitocina	Mes /Día /Hora				N/A (8)	39 dateoxy
40	Dilatación cervical al inicio de infusión con oxitocina	cm				N/A (8)	40 cervioxy
41	Puntaje de Bishop al inicio de infusión con oxitocina	puntos				N/A (8)	41 bishopoxy
42	Dosis total de oxitocina	IU				N/A (8)	42 dosetotal
43	Dosis (velocidad) máxima de oxitocina	mIU/min				N/A (8)	43 maxrate
44	Duración de infusión con oxytocina	min (hora min)				N/A (8)	44 timeoxy
45	Duración a la máxima velocidad de infusión	min (hora min)				N/A (8)	45 timemax
46	Sufrimiento fetal	(1) Sí	(0) No				46 distress
47	Pre-Eclampsia / Eclampsia	(1) Pre-eclampsia	(2) Eclampsia	(0) No			47 eclampsia
48	Hiperestimulación uterina	(1) Sí	(0) No				48 hyperstimu
49	Ruptura uterina	(1) Sí	(0) No				49 ruptureut
50	Desprendimiento prematuro de placenta	(1) Sí	(0) No				50 abruption
51	Laceración cervical (traumatismo del aparto genital)	(1) Sí	(0) No				51 laceration
52	Laceración perineal (grado)	(1) Sí grado	(0) No				52 tear
53	Atonía uterina	(1) Sí	(0) No				53 atony
54	Extracción manual de la placenta (Placenta retenida)	(1) Sí	(0) No				54 retain
55	Transfusión sanguínea	(1) Sí	(0) No				55 transfusion
56	Admisión a unidad de cuidados intensivos materna	(1) Sí	(0) No				57 icu
57	Muerte materna	(1) Sí	(0) No				56 mdeath
58	Sexo de recién nacido	(1) Masclino	(2) Femenino				57 sex
59	Apgar	1 min /5 min /10 min					58 apgar , ,
60	Peso de recién nacido	g					59 babywt
61	Talla de recién nacido	cm					60 babyht
62	Cirucumferencia de cabeza	cm					61 head
63	Circumferencia de pecho	cm					62 chest
64	Admisión a unidad de cuidados intensivos neonatal	(1) Sí	(0) No				63 ncu
65	Nacido muerto o muerte neonatal	(1) Sí	(0) No				64 ndeath