

# Poor Uterine Contractility as Maternal Predisposition to Postpartum Hemorrhage Among Low-Risk Women: An Analysis of Large-Scale Database

Keiko Nishida (✉ [keiko\\_creamstew@yahoo.co.jp](mailto:keiko_creamstew@yahoo.co.jp))

University of Tsukuba <https://orcid.org/0000-0003-0843-1721>

**Toshimi Sairenchi**

Dokkyo Ika Daigaku

**Koji Uchiyama**

Dokkyo Ika Daigaku

**Yasuo Haruyama**

Dokkyo Ika Daigaku

**Mariko Watanabe**

Dokkyo Ika Daigaku

**Hiromi Hamada**

Tsukuba Daigaku

**Toyomi Satoh**

Tsukuba Daigaku

**Susumu Miyashita**

Dokkyo Ika Daigaku

**Ichio Fukasawa**

Dokkyo Ika Daigaku

**Gen Kobashi**

Dokkyo Ika Daigaku

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## Research article

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## Abstract

**Background** Postpartum hemorrhage (PPH) is a major cause of maternal mortality. Even seemingly low-risk women may suddenly develop postpartum hemorrhage, and these cases are often unpredictable and threaten maternal life. We hypothesized that innate poor uterine contractility may be a risk factor of PPH. In this study, we examined the association between the innate poor uterine contractility, suggested by the characteristics of labor and PPH in obstetrically low-risk women.

**Methods** We used the Japan Perinatal Registry database of the Japan Society of Obstetrics and Gynecology registered in 2013–2016. With exclusion of women with well-known risk factors for PPH (maternal basal disease of hematologic disease, uterine leiomyoma, pregnancy by assisted reproductive technology, placenta abruption, placenta accrete, low-lying placenta, hypertensive disorders of pregnancy, macrosomia, polyhydramnios, or epidural analgesia), we analyzed 174,082 primiparous women who had one live singleton birth via vaginal delivery in cephalic presentation at 37 weeks' gestation. Information about abnormal labor patterns (hypotonic uterine dysfunction, prolonged labor, and arrest of labor) diagnosed by obstetricians were also used in this study. In order to focus on innate maternal poor uterine contractility, we classified subjects into four classes according to whether they were diagnosed with abnormal labor patterns and whether they had used uterotonics, and Odds ratios and their 95% CI were calculated as well.

**Results** Among the enrolled women, 10,508 (6.0%) had PPH. Abnormal labor patterns, including hypotonic uterine dysfunction (adjusted OR 1.28, 95% CI 1.22 to 1.34), prolonged labor (adjusted OR 1.41, 95% CI 1.30 to 1.52) and arrest of labor (adjusted OR 2.02, 95% CI 1.78 to 2.29) were significantly associated with an increased risk of PPH. Compared to women who were not diagnosed any abnormal labor patterns and did not use any uterotonics, women who were diagnosed with abnormal labor patterns were at a significantly increased risk for PPH regardless of whether they had used uterotonics (adjusted OR 1.23, 95% CI 1.10 to 1.37) or not (adjusted OR 1.30, 95% CI 1.23 to 1.37).

**Conclusion** Our study suggests that innate poor uterine contractility is a significant predisposing risk factor in otherwise low-risk women.

**Trial Registration:** This study is retrospectively registered.

## Background

Postpartum hemorrhage (PPH) is a major cause of maternal death worldwide [1, 2]. The incidence of PPH is reported to be 2–8% of all deliveries [3–6]. Multiparity, multiple pregnancies, macrosomia, polyhydramnios, hypertensive disorders of pregnancy, uterine leiomyoma, assisted reproduction technology (ART), maternal hematologic disease, and abnormal placentation, such as placenta previa and placental abruption, are well recognized as risk factors for PPH [6–10]. These risk factors could be identified by maternal medical history, maternal check-ups, or ultrasound examinations before labor starts. Meanwhile, the most common etiology of PPH was uterine atony [11, 12], which accounts for 70%–80% of PPH cases [13, 14]. Seemingly obstetrically low-risk women who do not have any of the above-mentioned risk factors may suddenly develop atonic PPH. These cases are difficult to predict and can lead to maternal death, which is a worrisome concern for both clinical mothers and obstetricians. They become especially critical in understaffed clinics with poor medical resources, where beginning blood transfusion immediately is difficult [15].

Many previous studies reported that induction and augmentation of labor are associated with PPH [16, 17]. Furthermore, Grotegut et al. [18] found an association between women with severe PPH secondary to uterine atony and greater amounts of oxytocin exposure. Medical indications for induction of labor include prevention of the risks associated with the prolongation of pregnancy, such as preeclampsia, fetal growth restriction (FGR), oligohydramnios, premature rupture of membrane (PROM), or the absence of spontaneous labor near post-term pregnancy. Similarly, the medical indications for the augmentation of labor include hypotonic uterine dysfunction and prolongation of the latent phase. Thus, the absence of spontaneous labor at term, hypotonic uterine dysfunction, and prolongation of latent phase may be caused by innate poor uterine contractility in the pregnant women. Therefore, we hypothesized that innate poor uterine contractility may be a risk factor of PPH, even in seemingly low-risk cases without the above-mentioned well-known risk factors. To date, no studies have been focused on innate uterine contractility to verify its association with the risk of PPH. In this study, we analyzed the association between the innate poor uterine contractility (suggested by the characteristics of labor) and PPH in obstetrically low-risk women, using the data from the Japan Perinatal Registry database.

## Methods

In this study, we used the Japan Perinatal Registry database, which is managed by the Japan Society of Obstetrics and Gynecology (JSOG). The database is a national collaboration of obstetric departments that started in 2001 and includes live births and stillbirths at 22 weeks or later. Standardized formats were given to obstetricians to enter the data, including information about maternal characteristics, maternal basal disease, complications of pregnancy, delivery characteristics, and neonatal outcomes, of all who gave birth at their own facility. In 2013, contents registered in the database were significantly changed to be more detailed clinically than before. Therefore, we used the data of 890,652 registered births between 2013–2016 from this database, which covers 22.1% of the total 4,016,010 live births and stillbirths in Japan from 2013–2016. During that period, 300 facilities participated in the registration in 2013, 355 facilities in 2014, 385 facilities in 2015, and 395 facilities in 2016.

We used data of maternal characteristics (maternal age; history of treatment for infertility; height; body weight before pregnancy; gestational weight gain), delivery characteristics (gestational age and neonatal birth weight), medical interventions for delivery (mechanical methods for ripening cervix,

which include balloon catheter or laminaria tents; uterotonics use; instrumental delivery, which include forceps or vacuum extraction) and pregnancy complications (gestational diabetes mellitus (GDM), FGR, non-reassuring fetal status (NRFS), PROM and intra amniotic infection (IAI) ). Furthermore, information of abnormal labor patterns (hypotonic uterine dysfunction, prolonged labor, and arrest of labor) diagnosed by obstetricians were also used in this study. These abnormal labor patterns were diagnosed according to the following definition by JSOG. 1) Hypotonic uterine dysfunction: when the intrauterine pressure is less than 10 mmHg at the cervical dilatation of 4 to 8 cm and less than 40 mmHg at the cervical dilatation of 9 cm in the second stage of labor. It is also used as a name of clinical presentation and refers to a condition in which labor does not progress due to inadequate uterine contraction. 2) Prolonged labor: when the baby does not deliver within 30 hours in the nulliparous women and 15 hours in the multiparous women, after the contraction cycle is within 10 minutes. 3) Arrest of labor: after the onset of labor, labor is progressed once, but labor has not progressed (no cervix dilation or descent the fetal head) for more than 2 hours despite the same uterine contraction. These data conform to the uniform coding specifications and have passed rigorous quality checks.

PPH was defined as having a blood loss  $\geq 1,000$  mL within 2 hours after delivery or requiring the use of a blood transfusion.

Maternal characteristics, delivery characteristics, and pregnancy complications were compared between PPH cases and controls who were not PPH, which were statistically assessed by using chi-square tests for categorical variables and t-test for continuous variables. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated. Moreover, multivariable ORs were also calculated by logistic regression adjusted for maternal age, treatment for infertility, pre-pregnancy BMI, gestational weight gain, gestational age, neonatal birth weight, cervical ripening, GDM, FGR, NRFS, PROM, and IAI. A p value  $\leq 0.05$  was considered to indicate statistical significance. Then, in order to focus on maternal innate poor uterine contractility, we classified subjects into four classes according to whether they were diagnosed abnormal labor patterns and whether they had used uterotonics, and ORs and their 95% CI were calculated as well. For multiple comparisons, a Bonferroni correction was made, and statistical significance was defined as a value of  $P < 0.0167$  (Bonferroni correction as  $0.05 / 3$  tests). Statistical analyses were performed using IBM SPSS Statistics, version 25.0 (Armonk, NY: IBM Corp.).

## Results

There were 10,508 PPH cases (6.0%) among a total of 174,082 low-risk women analyzed. Maternal characteristics, labor/delivery characteristics, abnormal labor patterns and pregnancy complications are shown in Table 1. Chi-square tests were conducted to compare data of controls and PPH cases. Maternal age  $\geq 35$  years (25.2% vs 19.8%,  $P < 0.001$ ), infertility treatment (9.7% vs 7.9%,  $P < 0.001$ ) and pre-pregnancy BMI  $\geq 30$  (4.1% vs 1.8%,  $P < 0.001$ ) were significantly more likely in women with PPH cases than controls. Except for PROM, there were significant differences between women with PPH and controls in all variables of labor/delivery characteristics and pregnancy complications. Among them, only FGR was significantly lesser in controls (1.3% vs 2.6%,  $P < 0.001$ ). Table 2 shows the crude and adjusted ORs and 95% CI for the risk of PPH. In abnormal labor patterns, hypotonic uterine dysfunction (adjusted OR 1.28, 95% CI 1.22 to 1.34), prolonged labor (adjusted OR 1.41, 95% CI 1.30 to 1.52) and arrest of labor (adjusted OR 2.02, 95% CI 1.78 to 2.29) were significantly associated with the risk of PPH. The three medical interventions were also significantly associated. Table 3 shows the logistic regression analysis for risk of PPH associated with four classes classified by diagnosis of abnormal labor patterns and uterotonics use. Compared to women who were not diagnosed with any abnormal labor patterns and did not use any uterotonics, women who were diagnosed with abnormal labor patterns were at a significantly increased risk for PPH regardless of uterotonics use. These association were not eliminated by the adjusted multivariable logistic regression analysis (not use uterotonics: adjusted OR 1.23, 95% CI 1.10 to 1.37, and use uterotonics: adjusted OR 1.30, 95% CI 1.23 to 1.37). Women who were not diagnosed with any abnormal labor patterns, but used uterotonics, were also at an increased risk of PPH (adjusted OR 1.36, 95%CI 1.29 to 1.43).

Table 1

Comparison of maternal characteristics, delivery characteristics, abnormal labor patterns and pregnancy complications: controls versus PPH.

	Controls		PPH cases		<i>P value*</i>
	N= 163574(94.0%)		N= 10508(6.0%)		
<i>Maternal characteristics</i>					
Age (year)					
<20	5001	(3.1)	300	(2.9)	<0.001
20-34	126240	(77.2)	7558	(71.9)	
≥35	32333	(19.8)	2650	(25.2)	
Treatment for infertility					
None	150639	(92.1)	9491	(90.3)	<0.001
Induction of ovulation and/or AIH	12935	(7.9)	1017	(9.7)	
Pre-pregnancy BMI (kg/m <sup>2</sup> )					
<18.5	33711	(20.6)	1632	(15.5)	<0.001
18.5-29.99	126860	(77.6)	8446	(80.4)	
≥30	3003	(1.8)	430	(4.1)	
Gestational weight gain (kg) **	10	± 4.36	11	± 4.85	<0.001
<i>Delivery characteristics</i>					
Gestational age (week)					
37-40	145011	(88.7)	8599	(81.8)	<0.001
>40	18563	(11.3)	1909	(18.2)	
Neonatal birth weight (g)					
<2500	11217	(6.9)	261	(2.5)	<0.001
2500-3499	139802	(85.5)	8083	(76.9)	
3500-3999	12555	(7.7)	2164	(20.6)	
Cervical ripening					
	11140	(6.8)	1055	(10.0)	<0.001
Uterotonics use					
	61873	(37.8)	5367	(51.1)	<0.001
Instrumental delivery					
	22894	(14.0)	2760	(26.3)	<0.001
<i>Abnormal labor patterns</i>					
Hypotonic uterine dysfunction					
	31293	(19.1)	2684	(25.5)	<0.001
Prolonged labor					
	7657	(4.7)	787	(7.5)	<0.001
Arrest of labor					
	1983	(1.2)	309	(2.9)	<0.001
<i>Pregnancy complications</i>					
GDM					
	6802	(4.2)	554	(5.3)	<0.001
FGR					
	4210	(2.6)	136	(1.3)	<0.001
NRFS					
	11976	(7.3)	879	(8.4)	<0.001
PROM					
	24792	(15.2)	1538	(14.6)	0.149
IAI					
	586	(0.4)	60	(0.6)	0.001
*chi-square test comparing controls and PPH cases.					
** t-test, mean ± Standard deviation.					
Abbreviations: AIH Artificial Insemination of Husband, BMI Body Mass Index, IAI Intra Amniotic Infection, FGR Fetal Growth Restriction, GDM Gestational Diabetes Mellitus, NRFS Non-Reassuring Fetal Status, PROM Premature Rupture Of the Membranes.					

Table 2  
Logistic regression analysis for risk of PPH associated with four factors.

	Univariable analysis				Multivariable analysis			
	Crude OR	95% CI			Adjusted OR*	95% CI		
<i>Maternal characteristics</i>								
Age (y)								
<20	1.00	0.89	-	1.13	1.02	0.91	-	1.15
20-34	<i>ref.</i>				<i>ref.</i>			
≥35	1.37	1.31	-	1.43	1.35	1.29	-	1.41
Treatment for infertility								
None	<i>ref.</i>				<i>ref.</i>			
Induction of ovulation and/or AIH	1.25	1.17	-	1.34	1.19	1.11	-	1.27
Pre-pregnancy BMI (kg/m <sup>2</sup> )								
<18.5	<i>ref.</i>				<i>ref.</i>			
18.5-29.99	1.38	1.30	-	1.45	1.25	1.18	-	1.32
≥30	2.96	2.64	-	3.31	2.56	2.27	-	2.89
Gestational weight gain (kg)	1.03	1.02	-	1.03	1.02	1.02	-	1.03
<i>Delivery characteristics</i>								
Gestational age (wk)								
37-40	<i>ref.</i>				<i>ref.</i>			
>40	1.73	1.65	-	1.83	1.35	1.28	-	1.42
Neonatal birth weight (g)								
<2500	0.40	0.36	-	0.46	0.44	0.39	-	0.51
2500-3499	<i>ref.</i>				<i>ref.</i>			
3500-3999	2.98	2.83	-	3.14	2.644	2.51	-	2.79
Cervical ripening	1.53	1.43	-	1.63	1.27	1.18	-	1.36
Uterotonics use	1.72	1.65	-	1.79	1.44	1.38	-	1.50
Instrumental delivery	2.19	2.09	-	2.29	2.05	1.95	-	2.15
<i>Abnormal labor patterns</i>								
Hypotonic uterine dysfunction	1.45	1.39	-	1.52	1.27	1.22	-	1.33
Prolonged labor	1.65	1.53	-	1.78	1.41	1.31	-	1.53
Arrest of labor	2.47	2.19	-	2.79	2.03	1.79	-	2.29
<i>Pregnancy complications</i>								
GDM	1.28	1.17	-	1.40	1.14	1.04	-	1.25
FGR	0.50	0.42	-	0.59	0.89	0.74	-	1.07
NRFS	1.16	1.08	-	1.24	1.17	1.09	-	1.26
PROM	0.96	0.91	-	1.02	0.98	0.92	-	1.03
IAI	1.60	1.22	-	2.09	1.42	1.08	-	1.86

\*Adjusted for maternal age, treatment for infertility, pre-pregnancy BMI, gestational weight gain, gestational age, birth weight, cervical ripening, GDM, FGR, NRFS, PROM, IAI.

Abbreviations: AIH Artificial Insemination of Husband, BMI Body Mass Index, IAI Intra Amniotic Infection, FGR Fetal Growth Restriction, GDM Gestational Diabetes Mellitus, NRFS Non-Reassuring Fetal Status, PROM Premature Rupture Of the Membranes.

Table 3  
Logistic regression: PPH risk associated with four classes between abnormal labor patterns and uterotonics use.

Diagnosis of abnormal labor patterns*	Uterotonics use	Controls	PPH cases	Univariable analysis			Multivariable analysis			
				Crude OR	95% CI	P value	Adjusted OR**	95% CI	p value	
(-)	x (-)	97002 (59.3)	4737 (45.1)	ref.			ref.			
(+)	x (-)	4699 (2.9)	404 (3.8)	1.76	1.58 - 1.96	<0.001	1.23	1.10 - 1.37	<0.001	
(-)	x (+)	32353 (19.8)	2750 (26.2)	1.74	1.66 - 1.83	<0.001	1.36	1.29 - 1.43	<0.001	
(+)	x (+)	29520 (18.0)	2617 (24.9)	1.82	1.73 - 1.91	<0.001	1.30	1.23 - 1.37	<0.001	
* Diagnosis of hypotonic uterine dysfunction, prolonged labor or arrest of labor.										
** Adjusted for maternal age, treatment for infertility, pre-pregnancy BMI, gestational weight gain, gestational age, neonatal birth weight, cervical ripening, GDM, FGR, NRFS, PROM, IAI and instrumental delivery.										
Abbreviations: BMI Body Mass Index, IAI Intra Amniotic Infection, CI Confidence Interval, FGR Fetal Growth Restriction, GDM Gestational Diabetes Mellitus, NRFS Non-Reassuring Fetal Status, OR Odds Ratio, PROM Premature Rupture Of the Membranes.										

## Discussion

The present results suggest that women with abnormal labor patterns are at a risk of PPH, regardless of uterotonics use. We assumed that innate poor uterine contractility lead to the reported abnormal labor patterns: hypotonic uterine dysfunction, prolonged labor, and arrest of labor.

Previous studies have reported that longer duration of labor, particularly during the second stage of labor, induction or augmentation of labor, or instrumental delivery, were independent risk factors for PPH [4, 7, 16, 19, 20]. Another study reported that women with PPH secondary to uterine atony were exposed to oxytocin for a longer duration of time and required higher maximal oxytocin dosing for delivery [18]. Additionally, one study reported that repeated dinoprostone vaginal insets increase the risk of PPH [21]. These previous reports were, in part, consistent with our findings. However no previous studies have focused on the innate uterine contractility and its role in PPH.

Our study is novel in that we examined the risk factor for PPH by separated according to the use of uterotonics and the diagnosis of abnormal labor patterns. In previous studies, it is unclear if the provided risk factors include both medical indications and medical interventions. For example, women with a longer duration of labor will be augmented by uterotonics. If the uterine contractility is still insufficient after the administration of uterotonics, more uterotonics may be required. It might be difficult to judge which one causes PPH. Therefore, medical indications and medical interventions should be considered separately.

The present results showed that women who were diagnosed with abnormal labor patterns in the first or second stage of labor had an increased risk of PPH, regardless of uterotonics use. This suggests that the administration of uterotonics alone might not be responsible for PPH. We hypothesized that an innate uterine dysfunction was underlying the abnormal labor patterns that were associated with PPH.

Uterine contraction in the third stage for postpartum hemostasis depends on two kinds of hormones, oxytocin and prostaglandins, as in the first and second stage. At the time of labor, oxytocin and prostaglandins bind to cell-surface receptors, causing depolarization of the uterine myocyte, which in turn promotes the opening of ligand-regulated calcium channels. Increased intracellular calcium activates myosin-light chain kinase, which activates myosin. Consequently, myocyte contractility is activated [23]. After delivery, myometrial fibers surrounding the maternal spiral artery of the placental bed contract owing to the oxytocin and prostaglandin stimulations, and then myometrial contraction compresses the spiral arteries and veins. As a result of myometrial contraction, the uterine walls strongly oppose one another. It is thought that these mechanisms regulate hemostasis in the third stage of labor [24]. During labor, oxytocin is released in pulses, increasing in both the frequency and duration of pulse as labor progresses [25]. Additionally, myometrial oxytocin receptor (OXTR) density increases throughout pregnancy [26]. Prostaglandins are potent stimulators of myometrial contractility, and among many prostaglandin classes, PGE<sub>2</sub> and PGF<sub>2</sub> are involved in uterine contractions. Large amounts of prostaglandins are released in the third stage of labor, and plasma levels of PGF<sub>2</sub> reach their maximum and start to decline within 10 minutes after placental separation [27]. These studies suggested that prostaglandins play an important role in securing hemostasis by way of myometrial contraction in the third stage of labor. In women with clinically abnormal labor patterns, we assumed that there is some dysfunction in the above described mechanisms. Namely, uterine contractility might be poor in the first two stages of labor (sometimes uterotonics may be required). Subsequently, in the third stage of labor, the myometrium intrinsically may not be able to contract, fails to respond to hemostatic regulation, which may result in PPH. Some pathogenic dysfunction may also play a role, including such as the synthesis dysfunction of oxytocin and prostaglandins or decreased sensitivity or expression of OXTRs, FP receptors, EP1 receptors, or EP3 receptors. Reinl et al. [28] have suggested that some OXTR gene variants are associated with increased oxytocin

responsiveness during labor. Grotegut et al. [29] reported that the genetic variation in OXTR and gene encoding G protein-coupled receptor kinase-6, which regulates desensitization of the OXTR, is associated with the amount of oxytocin required as well as the duration of labor.

Uterine fatigue and lactate accumulation in myometrium might also contribute to uterine dysfunction. Under muscle contraction, lactic acid is produced by glycolysis in all human cells. Under myometrium contraction during labor, lactate is produced, which leads to intracellular acidification. Intracellular acidification inhibits the calcium channels in myometrial cells and decreased intracellular calcium will lead to a weakening of the myometrial contraction [30, 31]. Thus, women diagnosed with abnormal labor patterns might include cases of lactate-induced uterine dysfunction.

Our findings suggested that women used uterotonics even in the absence of diagnosis of abnormal labor patterns had increased the risk of PPH. Aside from abnormal labor patterns, indications for use of uterotonics include HDP, FGR, PROM, post-term pregnancy, or prevention of macrosomia. Unfortunately, there are no indications for use of uterotonics in this database. In the obstetric clinical situation, oxytocic agents are routinely used in the first two stages. Previous studies have reported that prolonged or large amounts of oxytocin exposure, which may lead to the downregulation of OXTRs and failed uterine involution, results in PPH [6]. OXTR desensitization has been demonstrated in *in vitro* studies [32–34]. There is no consensus on whether prostaglandin use is a risk factor for PPH, however some studies have demonstrated an association between prostaglandin use and an increase risk for PPH [17, 35, 36]. One possible reason for increased PPH risk in women who used uterotonics without abnormal labor patterns may be due to the above-mentioned mechanisms.

In this study, we could use true low-risk subjects extracted from a large-scale clinical database certified by JSOG, defined as primiparous women who had live birth to singleton fetus via vaginal delivery in cephalic presentation at 37 weeks' gestation. For caesarean delivery, the amount of bleeding has been reported to be almost twice that of vaginal delivery [12, 14]. Some reasons for this result include: the effects of anesthesia, bleeding from a myometrial incision, active bleeding persisting after suture of the incision, or the effects of surgical procedures. Additionally, the amount of bleeding might include the amniotic fluid volume. Therefore, PPH after vaginal delivery and PPH after caesarean delivery should be assessed separately. Furthermore, we excluded women who had well-established risk factors for PPH, including coagulopathy, uterine leiomyoma, placental abruption, placenta accreta, low-lying placenta, polyhydramnios and HDP, which could be determined within the antenatal period [6, 9, 14, 17].

HDP is an independent risk factors for PPH, as previous studies have demonstrated [37, 38]. Particularly in preeclampsia, patients are usually hypovolemic, so they are more likely to receive blood transfusions than in those with a normal pregnancy [39]. In addition, angiogenic factors, which are strongly associated with an increased risk of preeclampsia, also play an important role in the clotting system through the activation of coagulation and vascular thrombosis [40]. Positive association between angiogenic factors and postpartum bleeding has been reported [37]. This is because women with HDP were excluded from this study.

Additionally, we excluded women who were administered epidural analgesia during labor. A meta-analysis of randomized trials comparing epidural with non-epidural analgesia in women in labor reported that epidural analgesia prolongs the second stage of labor and increases the likelihood of requiring an instrumental vaginal delivery [41]. The use of epidural analgesia may change the course of labor from the course of a woman's natural uterine contractility. On the other hand, the prolonged labor itself is also an indication for epidural analgesia. It is difficult to judge which of the above factors individually caused PPH. In Japan, only a few obstetric hospitals perform epidural analgesia, thus the rate of women who receive epidural analgesia during labor in Japan was only 6.1% [42]. Therefore, for generalizability in obstetric hospitals, women received epidural analgesia were excluded from this study.

In this study, we were able to use a sufficient sample size even after strict extraction and adjustment for several other risk factors for the analysis because of a large-scale database. There are no studies in Japan that have investigated the risk factors for PPH using such a large sample size. Furthermore, contrary to previous studies [18, 43], detailed information about the type of uterotonics allowed us to investigate their effects on PPH according to the type and number of uterotonics required during delivery.

However, this study had some limitations. First, this database is not a national registry, so, between 2013 and 2016, it covered only 22.1% of the total live births and stillbirths. Among the facilities registered in this database, the tertiary perinatal medical centers included 85 facilities in 2013, 87 facilities in 2014, 91 facilities in 2015, and 103 facilities in 2016, indicating that >70% of the facilities in this database are referral hospitals; hence the sample is not representative of all delivery cases. Second, there is no detailed information of the indication, timing, and dosage of uterotonics administration, including oxytocin and prostaglandins. Third, according to the ACOG reVITALize program [44], PPH was defined as cumulative blood loss  $\geq 1,000$  mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth progress regardless of route of delivery. In this database, however, the amount of bleeding within only 2 hours after delivery was registered and signs or symptoms of hypovolemia was not registered. Therefore, women with blood loss of  $\geq 1,000$  mL or women who received blood transfusion were defined as PPH cases to compensate for the above missing information.

## Conclusions

Our findings suggest that women with innate poor uterine contractility are predisposed to PPH wven with no other well-known risk factors, such as multiple pregnancies, polyhydramnios, preeclampsia, and hematologic disease.

Further studies are necessary to identify practical methods to predict the innate poor uterine contractility, such as genetic variants, which may make it possible to reduce the maternal mortality due to PPH.

## List Of Abbreviations

AIH; Artificial Insemination of Husband, ART; Assisted Reproductive Technology, BMI; Body Mass Index, CIs; Confidence Intervals, HDP; Hypertensive Disorders of Pregnancy, IAI; Intra Amniotic Infection, FGR; Fetal Growth Restriction, GDM; Gestational Diabetes Mellitus, JSOG; the Japan Society of Obstetrics and Gynecology, ORs; Odds Ratios, OXTR; Oxytocin Receptor, NRFS; Non-Reassuring Fetal Status, PROM; Premature Rupture Of the Membranes, PPH; Postpartum Hemorrhage.

## Declarations

### Ethics approval and consent to participate

The study protocol was reviewed and approved by the Bioethics Committee of Dokkyo Medical University (reference number: Daigaku 30014) and clinical research review subcommittee of JSOG (reference number: 92). The requirement for obtaining written informed consent from the patients was waived because the study utilized anonymized data from a database.

### Consent for publication

Not applicable

### Availability of data and materials

The data that support the findings of this study are available from the Japan Society of Obstetrics and Gynecology (JSOG) under license for the current study. Restrictions apply to the availability of these data and thus are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the JSOG.

### Competing interests

The authors declare that they have no competing interests.

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### Author' contributions

Keiko Nishida: Conceptualization, Investigation, Writing-Original Draft

Toshimi Sairenchi: Methodology, Formal analysis, Validation

Koji Uchiyama: Resources, Data curation

Mariko Watanabe: Writing – Review & Editing

Yasuo Haruyama: Formal analysis, Data curation

Hiromi Hamada: Methodology, Writing – Review & Editing

Toyomi Satoh: Writing – Review & Editing

Susumu Miyashita: Writing – Review & Editing

Ichio Fukasawa: Writing – Review & Editing

Gen Kobashi: Conceptualization, Supervision, Project administration, Writing – Review & Editing

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## Figures

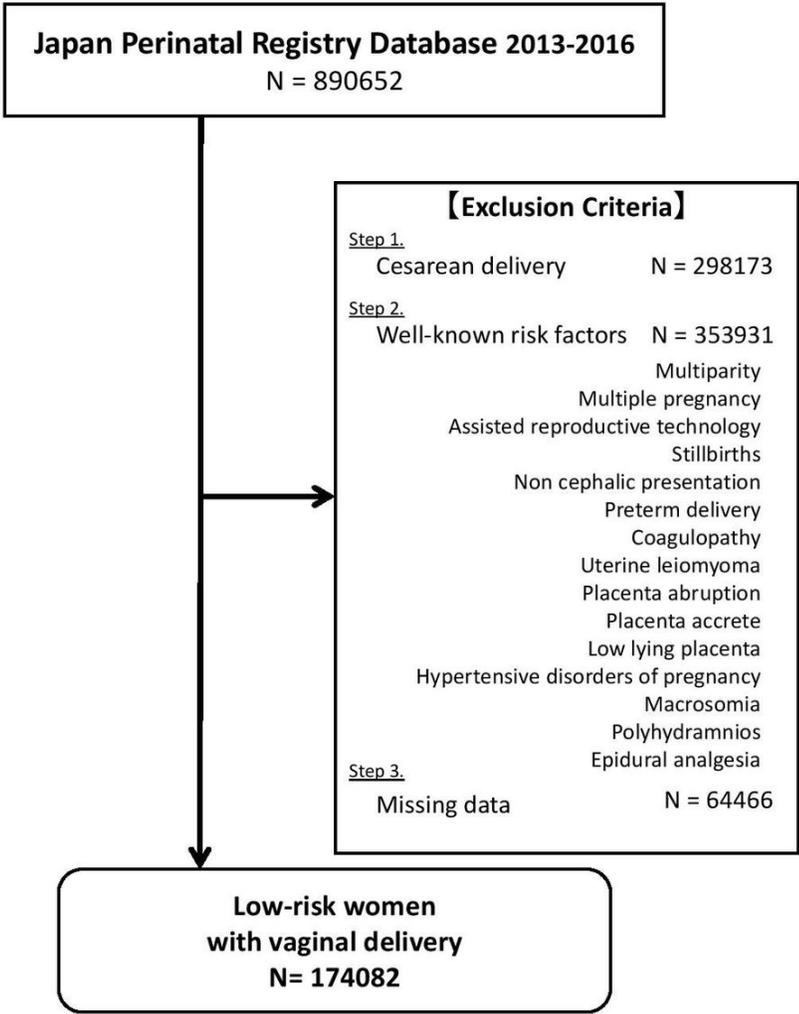


Figure 1

Selection of study population.