

In Vitro Fertilization Pregnancy is One of the Risk Factor for Atonic Bleeding in Problem-Free Pregnancy

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Received date: March 12, 2017; Accepted date: March 16, 2017; Published date: March 20, 2017

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Abstract

Background: To determine the risk factor for atonic bleeding in problem-free pregnancy.

Methods: A total of 898 cases of problem-free singleton pregnancies that vaginal delivered at ≥ 37 weeks of gestation were divided into a two groups based on the total amount of bleeding two hours after delivery: <800 ml group and >800 ml. The Mann-Whitney U-test was used for statistical analysis, and multivariate logistic regression analysis including the items showing a significant difference between the two groups was performed.

Results: Three factors, infant weight [Adjusted odds ratio (AOR) 1.002; 95% CI 1.001-1.003, $p<0.01$], instrumental labor [AOR 3.406; 95% CI 1.933-5.896, $p<0.01$], and *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) pregnancy [AOR 2.071; 95% CI 1.157-3.611, $p<0.01$] increased the risk of bleeding over 800 ml.

Conclusion: The instrumental labor and IVF/ICSI pregnancy increases the risk for atonic bleeding. It seems to be unrelated to other causes of bleeding related to these factors.

Keywords: Atonic bleeding; *In vitro* fertilization; Delivery; Instrumental labour

Introduction

Bleeding of over 500 ml within 24 h has been defined as abnormal PPH [1].

Recently, there have been many reports about PPH, which has increased in incidence worldwide with the reason remaining unclear [2,3].

However, this has recently been changed: over 800 ml is defined as abnormal obstetrical PPH, and over 1000 ml is defined as severe PPH in consideration of the mother's health and that emergency treatment is necessary, since 20% of maternal deaths after delivery are due to PPH in Japan [4]. Atonic bleeding accounts for 5% of bleeding in all deliveries.

Many risk factors for PPH during pregnancy have been previously reported [5-14]. There were also many reports of PPH risk during the stages of labor [1,15-24]. The existence of these factors suggests a risk for PPH before delivery, but abnormal PPH still occurs with a constant probability when these factors are absent.

There are many reports about the delivery risks of ART pregnancy, such as pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), and placental abnormalities during pregnancy [25-30] and at the time of delivery. Furthermore, operative delivery and PIH are increased after ART in women over 40 years old [31,32]. The risk of postpartum hemorrhage (PPH) is also thought to be greater after IVF pregnancy.

Because PPH can occur in pregnancies that have shown no problems, regardless of how pregnancy was achieved, it is clinically important to be able to predict PPH. In this retrospective study, the focus was on poor uterine contraction as a cause of PPH and multivariate analysis was used to evaluate the factors for atonic bleeding in problem-free pregnancies.

Materials and Methods

A total of 898 cases of problem-free singleton pregnancies that vaginal delivered at ≥ 37 weeks of gestation between January 2014 and January 2016 were included in this study.

The patients were divided into two groups based on the total amount of bleeding two hours after delivery: <800 ml and ≥ 800 ml. The Mann-Whitney U-test was used for statistical analysis. Multivariate logistic regression analysis including the items that were significantly different between the two groups was performed.

Birth canal damage, uterus varus, hysterorrhexis, retained placenta, placental adhesion, blood clotting abnormalities and so on were excluded as the causes of bleeding.

The groups were compared in terms of gestational week, maternal age, parity, maternal pre-pregnancy weight, maternal weight at delivery, maternal weight gain, maternal pre-pregnancy body mass index (BMI), maternal BMI at delivery, maternal BMI gain, maternal height, infant sex, infant weight, infant head circumference, presence or absence of medical intervention at delivery (induction of labor, vacuum extraction, forceps delivery or Kristeller maneuver), duration of labor, coiling of the umbilical cord, and treatment with IVF/ICSI. The level of significance was set at a p value of <0.05 .

Medical treatment during and after delivery was based on the Japan Society of Obstetrics and Gynecology criteria. To avoid the risk factors for PPH, the third stage of labor was within 30 min and no manual placental extraction and no retained placenta cases were included in this study. After the delivery of the placenta, if bleeding was over 500 ml, oxytocin was started to use to stop bleeding according to the guideline of the Japan Society of Obstetrics and Gynecology. When bleeding could not be stopped by oxytocin, uterine massage or methylergometrine was used. No cases required surgery.

Deliveries were performed by two board-certified obstetricians at the same facility. This study was conducted with the approval of the Ethics Committee of Yanaihara Women's Clinic and with patient consent (ERBY/1, 2014).

Results

Table 1 shows the differences in the clinical features between the blood loss at delivery <800 ml group and the >800 ml group. There were significant differences in ART pregnancies (14.5% vs. 32.9%), maternal age (33 years vs. 35 years), maternal BMI at delivery (24.3 kg/m² vs. 25.3 kg/m²), maternal BMI gain (3.7 kg/m² vs. 4.0 kg/m²), parity (38.9% vs. 2.7%), infant weight (3005 g vs. 3281 g), infant head circumference (32.6 cm vs. 33.2 cm), instrumental labor (11.5% vs. 35.4%), and the Kristeller maneuver (17.7% vs. 32.9%) (p<0.05).

	<800 ml (n=819)	≥ 800 ml (n=79)	p-value
Duration of labor (min)	578	716	p=0.08
IVF/ICSI	14.5% (119)	32.9% (26)	p<0.01
Maternal age (years)	33	35	p<0.01
Maternal BMI at delivery (kg/m ²)	20.5	21.3	p=0.20
Maternal BMI pre-pregnancy (kg/m ²)	24.3	25.3	p=0.02
Maternal BMI gain (kg/m ²)	3.7	4.0	p=0.02
Maternal height (cm)	159.1	158.8	p=0.77
Parity	38.9% (319)	2.7% (19)	p=0.03
Infant sex (male)	52.9% (433)	49.4% (39)	p=0.68
Infant weight (g)	3005	3281	p<0.01
Infant head circumference (cm)	32.6	33.2	p<0.01
Apgar score 1 min	8.7	8.5	p=0.17
Apgar score 5 min	9.5	9.5	p=0.81
Induction of labor	17.1% (140)	21.5% (17)	p=0.69
Instrumental labor	11.5% (94)	35.4% (28)	p<0.01
Kristeller maneuver	17.7% (145)	32.9% (26)	p=0.02
Coiling of the umbilical cord	14.2% (116)	13.9% (11)	p=0.99

Table 1: Comparison of blood loss during delivery using the average (800 ml) as a cutoff.

Table 2 shows the results of multivariate analysis to identify clinical features predictive of blood loss over 800 ml during delivery. After

applying Akaike's Information Criteria with the Forward Selection Method, 3 factors, infant weight [Adjusted odds ratio (AOR) 1.002; 95% confidence interval (CI), 1.001-1.003, p<0.01], instrumental labor [AOR 3.406; 95% CI, 1.933-3.611, p<0.01] and IVF/ICSI pregnancy [AOR 2.071; 95% CI, 1.157-3.611, p<0.01] were each found to increase the risk of bleeding over 800 ml independently.

	AOR	95% confidence interval	P-value
Infant weight (g)	1.002	0.385-0.811	p<0.01
Instrumental labor	1.803	1.155-2.796	p<0.01
IVF/ICSI	2.730	1.824-4.079	p<0.01
Parity	0.562	0.977-1.159	p<0.01

Table 2: Multivariate analysis of clinical features predictive of blood loss over 800 ml during delivery (AOR: Adjusted Odds ratio).

Discussion

In this country, it is performed in the medical practitioners that two-thirds deals with 3,000 cases from 100 a year of the parturient institution. The most are the hospitals of the small to middle with parturient number less than 1,000 in a year. Under this situation, we foresee an intranatal trouble beforehand, and it is important to be able to deal quickly. PPH has recently been increasing worldwide [2,33-35] and it has been reported that there are racial differences [4]. However, these reports do not provide any definitive reasons. Many risk factors for PPH during pregnancy have been previously reported [5-14]. There were also many reports of PPH risk during the stages of labor [1,15-24]. The existence of these factors suggests a risk for PPH before delivery, but abnormal PPH still occurs with a constant probability when these factors are absent.

In this study, a tendency similar to that in a past report was shown, and the risk of atonic bleeding was found to be related to infant weight, instrumental delivery and IVF/ICSI pregnancy independently.

The association of greater infant weight with poor contraction of the uterus has already been reported [19,22]. Although the indications for instrumental delivery have to be considered in detail, obstructed labor is the most common reason. In other words, this suggests that poor contraction of labor induces atonic bleeding.

IVF pregnancy is one cause of atonic bleeding, with a risk 2.7 times higher than that of spontaneous pregnancy (SP). This result excludes other factors causing PPH and proves that IVF pregnancy itself has an increased risk of atonic bleeding.

As lifestyles have changed with social conditions, so has the timing of marriage, which is now much later in a woman's life, thus delaying childbearing. Since the success of *in vitro* fertilization (IVF) in 1978, many children have been born this way. In Japan, pregnancy occurs at an advanced age, which is rare in the world, and assisted reproductive technology (ART) exceeds 40% in women 40 years or older. At present, one in 27 pregnancies is the result of *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI). In 2005, the rate of frozen embryo transfer cases increased, with a five-fold increase in the amount of cases between then and 2012 [36]. This fact suggests that people want to have their next baby using eggs that have been harvested at a younger age. The delivery risk, of course, increases with the tendency to marry later.

Healy et al. also reported causes of bleeding but did not mention atonic bleeding; however, there is much PPH with singleton births after IVF/ICSI. An exploratory analysis of factors in the IVF/ICSI group, showing associations with fresh embryo transfers in stimulated cycles, endometriosis, and hormone treatments, suggests that events around the time of implantation may be responsible, and that suboptimal endometrial function is the critical mechanism [12]. In terms of increased PPH after IVF, Aziz et al. reported that patients who conceived after receiving oocyte donation without controlled ovarian hyperstimulation were at increased risk for manual placental extraction, and this association was not affected by age differences between groups. However, this may be only one reason for the increased PPH [37]. In addition, reactivity of the uterus to oxytocin may decrease with aging and may be a cause of bleeding [23].

No report involving patients with sterility and oxytocin/oxytocin receptors was found in our search of the literature. The fact that there are many oxytocin unresponsive cases may suggest some relationship between sterility and oxytocin/oxytocin receptors, which may be worth researching [38].

The result of our analysis relates to atonic bleeding in general and the placental factor was excluded. Many articles recently described the need for exercise after delivery and during pregnancy [39-48].

We have reported that there is much medical intervention at the time of delivery after IVF pregnancy compared to the spontaneously gestation group and suggested that muscle weakness of the IVF patient is one of the related factors (in press). Especially after IVF treatment, patients tend to take a physical rest because they think that physical activity causes miscarriage and premature labor. Additionally, it has been found that human body function decreases as life becomes more convenient with technological progress. In other words, muscle weakness that occurs due to decreased exercise levels may be a cause of bleeding. Thus, it is important that pregnant women understand the importance of physical activity. Therefore, it is conceivable that muscle hypofunction may be the cause of increased PPH, especially atonic bleeding, worldwide. Further study is necessary to identify the cause of increased PPH.

Conclusion

Clinically, if three factors are present (IVF pregnancy, instrumental delivery, and infant over 3014 g in this county), uterine constrictors must be given without hesitation and bleeding must be treated immediately.

A prospective study is being planned for the future.

Acknowledgement

We thank Dr. Luba Wolchuk who provided medical writing services on behalf of Forte Inc.

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