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Evaluation of the effect of dinoprostone vaginal ovule for cervical maturation and labor induction in term pregnancies on the duration of the third stage of labor and amount of postpartum bleeding

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Ethics Committee Approval
The study was approved by Clinical Research Ethics Committee of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (2011-KAEK7-25, 2020/09-02).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Postpartum bleeding is a leading preventable cause of maternal death. Prolonged 3rd stage duration of labor and induction agents can increase postpartum bleeding. This study evaluated the effect of using a dinoprostone (PGE2) vaginal insert, a cervical ripening and labor induction agent, on the 3rd stage duration of labor and the amount of postpartum bleeding.
Methods: This prospective cross-sectional study involved 301 patients with vaginal delivery between 01.10.2020 and 30.06.2021. Patients were separated into two groups: PGE2+oxytocin (Group A) and only oxytocin (Group B). They were compared in terms of prepartum and postpartum data, 3rd stage duration of labor, and the amount of blood loss in the first 18 h postpartum.
Results: The median 3rd stage duration of labor was 8 min in Group A and 7 min in Group B (P=0.009). No significant differences were found between the groups in the amount of postpartum blood loss, percentage changes in hemoglobin and hematocrit values, or when patients were analyzed based on 3rd stage duration of labor (≤10 vs. >10 min). Severe postpartum hemorrhage (≥1000 ml) was associated with decreased gravida, increased body mass index, longer oxytocin use, and prolonged 3rd stage duration of labor in all patients. In Group A, severe postpartum hemorrhage was associated with decreased gravida, increased body mass index, and longer duration of PGE2 use.
Conclusion: PGE2 prolonged the 3rd stage duration of labor, but this did not increase postpartum bleeding compared to oxytocin. However, an increase in the duration of PGE2 use was associated with postpartum hemorrhage. Therefore, shortening the duration may be considered in patients with additional risk for postpartum hemorrhage.

Keywords: dinoprostone, 3rd stage duration of labor, postpartum hemorrhage, labor induction and augmentation

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Introduction

Every year, hundreds of thousands of women worldwide die from mostly preventable complications related to pregnancy and childbirth. In 2017, 295,000 female deaths were reported due to such complications [1]. Unfortunately, most of these deaths occur in developing countries with limited resources, insufficiently experienced healthcare providers, and inadequate emergency delivery services [2].

Maternal mortality refers to the death of a woman during pregnancy or within 42 days after delivery due to the pregnancy itself or its management or caused by any reason that is aggravated by these, regardless of the duration and location of the pregnancy. While maternal mortality is a significant concern, maternal morbidity is a more common condition that is just as important. Women face acute or chronic morbidity, with sequelae that can impair their life functions, approximately 20–30 times the maternal mortality rate, due to pregnancy and childbirth complications [3]. These sequelae can negatively impact a woman's physical, mental, or sexual health, body image perception, and social and economic status [4].

Postpartum hemorrhage is the leading preventable cause of maternal mortality and morbidity worldwide. Despite modern medical advancements, approximately one-fifth of maternal deaths are still linked to postpartum hemorrhage, with an even higher incidence in low socio-economic countries. The World Health Organization (WHO) defines postpartum hemorrhage as 500 ml or more bleeding within the first 24 h after birth. If the bleeding is 1000 ml or more, it is categorized as severe postpartum bleeding [5]. The incidence of postpartum hemorrhage varies worldwide due to different diagnostic criteria and methods of measuring blood loss. Studies based on estimated blood loss report rates of postpartum hemorrhage between 1–3% [6,7], whereas those based on quantitative measurement indicate that the rate may be as high as 10% [8]. The 3rd stage of labor is a significant factor in postpartum bleeding, with longer durations increasing the risk of hemorrhage. The 3rd stage duration of labor varies between 6 and 30 min, with an average blood loss of approximately 150–250 ml [9]. Patients whose placenta separates within the first 10 min tend to experience the least bleeding [10].

Prevention and treatment of postpartum hemorrhage is a globally accepted necessity. Identifying patients at high risk for postpartum hemorrhage, interventions to prevent bleeding, early diagnosis in case of bleeding, and timely management with appropriate resources all play an essential role in preventing maternal mortality and morbidity.

Dinoprostone (PGE2) vaginal ovule is a commonly used pharmacological agent for cervical ripening and labor induction in pregnant women who require delivery but are not suitable for induction of labor with oxytocin due to a low Bishop score on vaginal examination. One of the causes of postpartum hemorrhage is the duration of the 3rd stage of labor, including prolongation of placental separation and the presence of residual placental tissue in the uterus. Literature studies have shown that the risk of postpartum hemorrhage increases as the duration of the 3rd stage of labor lengthens. This study aims to evaluate the effect of using PGE2 vaginal ovule for cervical ripening and labor induction in term pregnant women on the duration of the 3rd stage of labor and the amount of postpartum bleeding.

Materials and methods

This prospective, cross-sectional, and single-center study was initiated after obtaining approval from the Clinical Research Ethics Committee of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (approval numbers: 2011-KAEK7-25 and 2020/09-02). The study included 301 pregnant patients aged between 18 and 45 years, with term pregnancy ranging from 37 to 42 weeks, who met the inclusion criteria and were admitted to the delivery room for labor induction or augmentation between October 1, 2020, and June 30, 2021, and delivered vaginally. The study group (Group A) comprised pregnant women who received oxytocin after applying and withdrawing PGE2 vaginal ovules, while the control group (Group B) comprised pregnant women who did not receive PGE2 vaginal ovules and only received oxytocin.

The study's exclusion criteria were pregnancy before 37 weeks, multiple pregnancies, absence of fetal head presentation, history of placental retention in previous deliveries, history of three or more curettages, history of previous cesarean section or uterine surgery, stillbirth due to in-utero ex fetus, diagnosis of hypertensive disorders of pregnancy in antenatal follow-ups, placental abruption, a vaginal or cervical laceration that could increase the amount of postpartum bleeding, hematological disease or drug use that could increase postpartum bleeding, and not having a vaginal delivery. Patients were informed about the study, and their consent was obtained.

The following information was recorded: age, gravida, gestational age (days), parity, weight, and height. Vaginal ovules containing 10 mg PGE2 (Prostaglandin E2) were administered to patients with a Bishop score ≤5, provided there were no contraindications. After sufficient cervical maturity was reached, labor began, or the maximum usage time was reached, the ovule was withdrawn, and oxytocin infusion was started 30 min to 1 h later. Patients who had vaginal delivery were included in the study group. Patients with a Bishop score >5 did not receive PGE2 vaginal ovules; only oxytocin infusion was applied. Patients who had vaginal delivery were included in the control group.

Oxytocin infusion was prepared by adding 5 units of oxytocin to 500 ml of Ringer's lactate, started as an intravenous infusion of 4 milliunits/min, and increased by 2 milliunits every 20 min until the adequate uterine contraction was achieved. The maximum dose was 20 milliunits/min. Oxytocin was started as an augmentation application for pregnant women who did not enter active labor and for pregnant women who were in active labor but did not have a sufficient uterine contraction.

The study and control groups' third-stage duration of labor, prenatal hemoglobin and hematocrit values, hemoglobin and hematocrit values at the 6th and 18th h after birth, baby gender, birth weight, 1st and 5th min APGAR scores, newborn intensive care hospitalization, need for erythrocyte transfusion, and postpartum curettage requirement was recorded. The third stage, duration of labor, is the period from the baby's delivery to the placenta's delivery. Controlled cord traction was not applied until signs of placental separation were observed during this period. When the spontaneously separated placenta came to the

vagina, it was removed with cord traction. Manual extraction was applied for the placentas that did not come out within the first 30 min. As postpartum bleeding prophylaxis, 10 U oxytocin infusion in 500 ml Ringer's lactate was administered after the baby's delivery, and 0.2 mg methylergonovine was intramuscularly administered after the delivery of the placenta.

The volume of blood loss at the postpartum 18th h was calculated in ml according to the postpartum blood loss calculation formula, using the patient's height, weight, and prenatal and postpartum 18th-h hematocrit values. Statistical methods were used to compare the data and results of both groups.

Statistical analysis

The distribution of variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. For normally distributed variables, independent samples t-tests were used to compare the two groups, and for non-normally distributed variables, the Mann-Whitney U test was used for independent samples, while paired samples t-tests and Wilcoxon signed-rank tests were used for normally and non-normally distributed dependent variables, respectively. Descriptive statistics were presented as mean (standard deviation) for normally distributed data and median (minimum-maximum) for non-normally distributed data. Categorical variables were reported as numbers (%), and comparisons between groups were made using Pearson's chi-square, Fisher's exact, and Fisher-Freeman-Halton tests. The Spearman rank correlation coefficient was used to examine the relationships between variables. The Backward method was employed in binary logistic regression analysis to identify risk factors. Percentage change values were calculated to compare the changes in hemoglobin and hematocrit levels at the 6th and 18th h relative to the first measurement between the groups [Percent change = (last measurement - first measurement) / first measurement]. All statistical analyses were performed using SPSS version 22.0, and a significance level of α=0.05 was used.

Results

Table 1 compares demographic data and postpartum findings between study participants. The duration of oxytocin use and the 3rd stage duration of labor showed statistically significant differences between the groups (P=0.048 and P=0.009, respectively). In Group A, the median duration of oxytocin use was shorter (130 min), while the median duration of the 3rd stage of labor was longer (8 min). No relationship was observed between the duration of PGE2 use and the amount of blood loss (r=0.102, P=0.215). No significant differences were observed between the groups for the other variables listed in Table 1.

For all patients, the median hemoglobin and hematocrit levels measured prepartum were higher than those measured at the 6th and 18th h postpartum (P<0.001 for each), as shown in Table 2. The prepartum hemoglobin and hematocrit levels in both groups were significantly higher than the postpartum 6th and 18th-h measurements (P<0.001 for each), as shown in Table 2.

Groups A and B were further divided into two subgroups based on the 3rd stage duration of labor, i.e., ≤10 min and >10 min. The subgroups were compared regarding the blood loss amount and percentage changes in hemoglobin and hematocrit levels at the 6th and 18th h postpartum. No significant differences were observed between Group A or B subgroups (Table 3).

Table 1: Comparison of demographic data and findings between groups

	Group A (n=151)	Group B (n=150)	*P*-value
Age (years)	26 (18:44)	25.5 (18:42)	0.596
Pregnancy period (weeks)	277 (259:294)	274 (259:290)	0.029
Gravida	2 (1:7)	2 (1:6)	0.706
Parity	1 (0:4)	1 (0:5)	0.383
BMI	29.21 (20.20:53.13)	28.18 (21.22:39.96)	0.243
Oxytocin usage time (min)	130 (20:985)	177.5 (15:1070)	0.048
3rd stage duration of birth (min)	8 (2:33)	7 (2:30)	0.009
3rd stage duration of birth (min)			
<=10 min	111 (73.5)	122 (81.3)	0.105
>10 min	40 (26.5)	28 (18.7)	
3rd stage duration of birth (min)			
0-10 min	111 (73.5)	122 (81.3)	0.234
11-20 min	37 (24.5)	25 (16.7)	
21 min and over	3 (2)	3 (2)	
Blood loss (ml)	486.2 (15:1657)	382.77 (26:1765)	0.054
Blood loss (ml)			
(0-500) ml	76 (50.3)	92 (61.3)	0.124
(500-1000) ml	57 (37.7)	47 (31.3)	
>=1000 ml	18 (11.9)	11 (7.3)	
Blood loss (ml)			
<1000 ml	133 (88.1)	139 (92.7)	0.249
>=1000 ml	18 (11.9)	11 (7.3)	
HGB-N6 n (%)*	-3.57 (-23.97:10.61)	-2.28 (-23.02:6.96)	0.465
HGB-N18 n (%)*	-4.02 (-25.14:12.66)	-2.71 (-22.08:7.58)	0.489
HCT-N6 n (%)*	-9.26 (-29.06:1.96)	-7.55 (-29.69:0)	0.107
HCT-N18 n (%)*	-8.77 (-28.13:-0.29)	-7.46 (-29.01:-0.47)	0.095
Baby gender n (%)			
Male	71 (47.3)	77 (51)	
Female	79 (52.7)	74 (49)	0.525
Birth weight (kg)	3243.9(374.65)	3168.44(409.68)	0.097
APGAR 1	9 (8:9)	9 (4:9)	0.161
APGAR 5	10 (7:10)	10 (8:10)	0.621
Blood transfusion n (%)			
No	150 (100)	150 (99.3)	
Yes	0 (0)	1 (0.7)	1.000
Postpartum intervention n (%)			
No	148 (98.6)	150 (99.3)	
Perform manual extraction	1 (0.7)	1 (0.7)	0.748
BUMM curettage	1 (0.7)	0 (0)	
NIC insertion n (%)			
No	146 (97.3)	139 (92.1)	0.074
Yes	4 (2.7)	12 (7.9)	

* In order to compare the groups, it was calculated by taking the percentage change of the measurements at the 6th and 18th h compared to the first measurement. Percent change = (last measurement-first measurement)/first measurement. BMI: Body Mass Index, n: number, HGB: Hemoglobin, HCT: Hematocrit, N: Newborn, NIC: Newborn Intensive Care

Table 2: Comparison of prepartum and postpartum hemoglobin and hematocrit values

	All Patients (n=301)		Group A (n=151)		Group B (n=150)	
		P-value		*P*-value		*P*-value
HGB (Prepartum)	11.9 (8.4:14.9)	<0.001	11.81(1.21)	<0.001	11.9 (8.4:14.1)	<0.001
HGB (Postpartum 6th h)	11.4 (7.7:14.60)		11.37(1.23)		11.5 (7.8:14.1)	
HGB (Prepartum)	11.9 (8.4:14.9)	<0.001	11.9 (8.4:14.9)	<0.001	11.9 (8.4:14.1)	<0.001
HGB (Postpartum 18th h)	10.8 (7.3:13.8)		10.8 (7.3:13.4)		10.6 (7.5:13.8)	
HCT (Prepartum)	35.9 (26.5:43.9)	<0.001	35.70(3.10)	<0.001	35.29(3.58)	<0.001
HCT (Postpartum 6th h)	34.5 (24.1:44)		34.33(3.32)		33.97(3.72)	
HCT (Prepartum)	35.9 (26.5:43.9)	<0.001	35.70(3.10)	<0.001	35.29(3.58)	<0.001
HCT (Postpartum 18th h)	32.3 (23.4:42.7)		32.17(3.25)		32.19(3.67)	

HGB: Hemoglobin, n: number, HCT: Hematocrit. The values given are given as mean (standard deviation) in normally distributed data or median (minimum:maximum) in non-normally distributed data, according to data distribution.

To identify factors associated with a risk of blood loss ≥1000 ml in all patients, a Binary Logistic Regression Analysis using the Backward method was conducted on the variables of the group, gravida, parity, body mass index (BMI), oxytocin duration, and the 3rd stage duration of labor (Table 4). Gravida, BMI, oxytocin duration, and the 3rd stage duration of labor were statistically significant. In all patients, a decrease of 1 unit in gravida was associated with a 2.141 (1/0.467) times higher risk of blood loss ≥1000 ml (P=0.002); an increase of 1 unit in BMI was associated with a 1.101 times higher risk of blood loss ≥1000 ml (P=0.017); an increase of 1 unit in oxytocin duration was associated with a 1.003 times higher risk of blood loss ≥1000 ml (P=0.002); and an increase of 1 unit in the 3rd stage duration of

labor was associated with a 1.094 times higher risk of blood loss ≥1000 ml (P=0.038).

To investigate the factors associated with a risk of blood loss ≥1000 ml in Group A, a Binary Logistic Regression Analysis using the Backward method was conducted on the variables of gravida, parity, BMI, oxytocin duration, PGE2 duration, and 3rd stage duration of labor. The gravida, BMI, and PGE2 duration variables were statistically significant (Table 4). In this group, a decrease of 1 unit in gravida was associated with a 2.762 (1/0.362) times higher risk of blood loss ≥1000 ml (P=0.008); an increase of 1 unit in BMI was associated with a 1.107 times higher risk of blood loss ≥1000 ml (P=0.040); and an increase of 1 unit in the duration of PGE2 use was associated with a 1.003 times higher risk of blood loss ≥1000 ml (P=0.019).

Table 3: Comparisons by duration of the 3rd stage of birth

	Group A (n=151)			Group B (n=150)		
	≤10 min (n=111)	>10 min (n=40)	*P*-value	≤10 min (n=111)	>10 min (n=40)	*P*-value
Amount of Blood Loss (ml)	483.12 (36.72:1657.57)	553.69 (15.22:1289.59)	0.505	375.79 (61.21:1765.09)	424.32 (26.11:1496.3)	0.616
HGB-Dec6 (%)*	-3.28(6.39)	-4.36(6.52)	0.365	-1.9 (-23.02:6.96)	-3.7 (-17.5:3.48)	0.143
HGB-Dec18 (%)*	-3.29(6.61)	-4.74(7.03)	0.244	-2.1 (-22.08:7.58)	-4.57 (-20:3.03)	0.082
HCT-Dec6 (%)*	-9.09 (-29.06:1.96)	-9.95 (-26.45:0)	0.403	-7.66 (-29.69:0)	-7.43 (-27.56:-1.65)	0.889
HCT-Dec18 (%)*	-8.68 (-28.13:-0.62)	-9.98 (-27.30:-0.29)	0.650	-7.22 (-26.49:-1.03)	-7.8 (-29.01:-0.47)	0.714

* In order to compare the groups, it was calculated by taking the percentage change of the measurements at the 6th and 18th h compared to the first measurement. [Percentage change = (last measurement-first measurement)/first measurement], **The values given are given as mean (standard deviation) in normally distributed data or median (minimum:maximum) in non-normally distributed data, according to data distribution. HGB: Hemoglobin, HCT: Hematocrit, n: number. Dec: Decline

Table 4: Evaluation of risk factors for severe postpartum bleeding (≥1000 ml) in all patients and dinoprostone+oxytocin group by binary logistic regression analysis

		P-value	HR	95% CI.	
All Patients	Gravida	0.002	0.467	0.288	0.756
	BMI	0.017	1.101	1.017	1.191
	Oxytocin time	0.002	1.003	1.001	1.005
	3rd stage of birth	0.038	1.094	1.005	1.191
Group A	Gravida	0.008	0.362	0.171	0.765
	BMI	0.040	1.107	1.005	1.219
	Oxytocin time	0.053	1.003	0.999	1.005
	Dinoprostone duration	0.019	1.003	1.000	1.005

Both Models: P<0.001, BMI: Body Mass Index, CI: Confidence Interval/Confidence Interval, HR: Hazard Ratio

Discussion

The PGE2 vaginal ovule is a pharmacological agent frequently used to induce labor in pregnant women admitted for induction due to low Bishop scores in the vaginal examination and unsuitability for induction with oxytocin. This study aimed to compare patients administered oxytocin infusion after PGE2 use with those given oxytocin infusion without PGE2 in terms of the 3rd stage duration of labor, postpartum blood loss, and postpartum hemoglobin and hematocrit values compared to prepartum measurements.

Although numerous studies have investigated PGE2 vaginal ovule, few have evaluated its effects on the duration of the 3rd stage of labor. Comb and Laros [11] evaluated 12,979 vaginal deliveries and found that the median duration of the 3rd stage of labor was 6 min, with placental separation occurring within the first 10 min in 75% of deliveries. The same study found that birth augmentation increased the 3rd stage duration of labor by 1.47 times. In a study by Mahboobeh Taebi et al. [12], which analyzed 1000 births, the median 3rd stage duration was 5 min, and labor induction increased the duration by 2.05 times. No previous study has shown a relationship between PGE2 vaginal ovule and the duration of the 3rd stage of labor. In our study, the median duration of the 3rd stage of labor was 8 min in Group A and 7 min in Group B, consistent with the literature. When the two groups were compared, the duration of the 3rd stage of labor was significantly higher in Group A. This finding suggests that further studies should investigate this relationship.

In a study by Eran Ashwal et al. [13], including 33,915 vaginal deliveries, labor induction was found to increase placental retention 1.84 times, and the labor induction rate with PGE2/prostaglandins was significantly higher in the group with placental retention compared to the group without. In a study by Favilli et al. [14], labor induction with prostaglandins was associated with a 4.29-fold increase in the risk of placental retention. However, our study found no significant difference between the groups regarding placental retention, which may be related to the small number of our patients. Although blood loss in the first 18 h postpartum was higher in Group A than in Group B in our study, this was insignificant. There was no difference between the two groups in the percentage changes of postpartum 6th and 18th-h hemoglobin and hematocrit values compared to prepartum values. In the study of Khireddin et al. [15], labor induction was associated with a higher risk of postpartum hemorrhage than spontaneous labor. According to the same study, oxytocin induction of labor increased the risk of postpartum hemorrhage 1.52 times, and prostaglandin induction increased the risk by 1.21 times. The risk of severe postpartum hemorrhage was 1.57 times higher with oxytocin induction and 1.42 times higher with prostaglandin induction. A meta-analysis comparing the use of intravenous oxytocin along with other methods for labor induction found no significant difference between the oxytocin group and the PGE2 vaginal ovule group regarding postpartum bleeding [16]. The findings of our study are consistent with the results of the meta-analysis.

In the literature, studies have shown that as the duration of the 3rd stage of labor increases, the amount and risk of postpartum hemorrhage also increase. In a study by Manon Van Ast et al. [10] that examined 7,203 single vaginal deliveries, the group with postpartum hemorrhage had a median duration of the 3rd stage of labor of 26 min, while the group without postpartum hemorrhage had a median duration of 10 min. There was a statistically significant difference between these values. The same study found that compared to the subgroup with a duration of the 3rd stage of labor <10 min, the incidence of postpartum hemorrhage increased 1.5 times in the subgroup with a duration of 10–19 min, 2.3 times with a duration of 20–29 min, 3.2 times in the subgroup with a duration of 30-39 min, and 4.6 times in the subgroup with a duration of 40–49 min. In the study of Frolova et al. [17], an increased risk of postpartum hemorrhage was found when the 3rd stage of labor was 20 min or more. In our study, we divided the duration of the 3rd stage of labor into two subgroups as ≤10 min and >10 min and compared them in terms of the amount of blood loss, percentage decreases of postpartum 6th and 18th-h hemoglobin and hematocrit values in both Group A and Group B. However, we did not find a significant difference between the subgroups.

Our study found that a prolonged 3rd stage of labor was associated with an increased risk of severe postpartum hemorrhage. This finding is consistent with previous studies that have reported an increased risk of postpartum hemorrhage with a longer 3rd stage duration of labor [10,17]. Additionally, our study found that an increase in BMI was associated with an increased risk of severe postpartum hemorrhage, which aligns with previous studies reporting obesity as a risk factor for postpartum hemorrhage [19]. Furthermore, we found that each unit increase in the duration of PGE2 use in Group A increased the risk of severe postpartum hemorrhage by 1.003 times. This result is consistent with a French study that found that repeated use of PGE2 vaginal ovule, especially over 30 h, was associated with postpartum hemorrhage [18]. Lastly, we found that a decrease in gravida was a risk factor for severe postpartum hemorrhage, whereas a study by Wetta et al. [19] found nulliparity as a risk factor for postpartum hemorrhage.

Since our study was conducted in a single center and the number of patients was limited, further studies with larger sample sizes are required to evaluate the effect of using PGE2 vaginal ovule in term pregnancies on the duration of the 3rd stage of labor and the amount of postpartum hemorrhage. However, given that PGE2 is commonly used, studies are scarce in the literature regarding its impact on the 3rd stage duration of labor and its correlation with postpartum hemorrhage. Hence, our study will provide valuable insights into this topic and contribute to the existing literature.

Conclusion

Our study suggests that using PGE2 prolongs the 3rd stage duration of labor. Given that prolonging the 3rd stage increases postpartum blood loss, active management of the 3rd stage of labor could be considered in pregnant women using PGE2. Additional interventions could accelerate the 3rd stage of labor in patients given PGE2 induction. However, due to the small number of patients in our study and the limited number of studies on this subject in the literature, definite recommendations cannot be made now. Nevertheless, the lack of a significant difference in blood loss between the groups suggests that PGE2 is a safe agent for cervical ripening and labor induction and does not increase the risk of postpartum hemorrhage. Clinicians and patients could benefit from additional precautions, and predicting that the risk of bleeding will increase in patients with risk factors such as decreased gravida, increased BMI, and prolonged induction time.

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