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SHORT REPORT

A strong association between human earwax-type and apocrine colostrum secretion from the mammary gland

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Abstract Here we provided the first genetic evidence for an association between the degree of apocrine colostrum secretion and human earwax type. Genotyping at the earwax-type locus, rs17822931 within the *ABCC11* gene, revealed that 155 of 225 Japanese women were dry-type and 70 wet-type. Frequency of women without colostrum among dry-type women was significantly higher than that among wet-type women ($P < 0.0002$), and the measurable colostrum volume in dry-type women was significantly smaller than in wet-type women ($P = 0.0341$).

Keywords Human earwax-type · Colostrum secretion · *ABCC11* · Polymorphism

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Short reports

Human earwax, a secretory product of ceruminous apocrine glands, is a dimorphic trait consisting of wet and dry types. We previously showed that a SNP (c. 538G > A, rs17822931) in the *ABCC11* gene is the earwax-type determinant: AA genotype gives dry-type and others wet-type (Yoshiura et al. 2006). As both colostorum and cerumen have a common origin of the secretory glands (Jirka 1968; Petrakis et al. 1975), human earwax type is suggested to be associated with colostrum secretion.

To test this hypothesis, we compared the degree of colostrum secretion to earwax types. The colostrum was obtained from 225 Japanese women on the first postpartum day by 10-min milking both their breasts, and its volume was measured by midwives. Genotyping at rs17822931 was performed as described previously (Yoshiura et al. 2006). The midwives were blind to earwax type of any participants, while obstetricians were also blind to any information on the colostrum secretion status prior to genotyping. All study protocols were approved by IRB, and written informed consent was obtained from all participants. Ninety-two women secreted 0.1–20 ml of colostrum, while the remaining 133 women did not give any recognizable amount of colostrum. Neither the frequency of wet-earwax women without secretion nor the time from delivery to milking differed between 108 primipara and 117 multipara women (data not shown). Genotyping at rs17822931 revealed that 155 of the 225 women were AA homozygotes (dry-type) and 70 GA heterozygotes or GG homozygotes (wet-type). Women in the two groups had no significantly different cesarean-section rates: 33.5% (52/155) of dry-type women versus 38.6% (27/70) of wet-type women ($P = 0.546$, Fisher's exact test). The frequency of dry-type women without colostrum secretion (105/155 or 67.7%)

Table 1 Distribution of dry-type and wet-type women with or without colostrum secreted 24–36 h after delivery

	No. of women examined	No. (%) of women with		*P* value
		No secretion	Colostrum secreted[a]	
All women				
Dry-type	155	105 (67.7)[b]	50 (32.3)[b]	0.000127
Wet-type	70	28 (40.0)	42 (60.0)	
Total	225	133	92	
Primipara				
Dry-type	78	55 (70.5)[b]	23 (29.5)[b]	0.0019
Wet-type	30	11 (36.7)	19 (63.3)	
Total	108	66	42	
Multipara				
Dry-type	77	50 (64.9)[b]	27 (35.6)[b]	0.0297
Wet-type	40	17 (42.5)	23 (57.5)	
Total	117	67	50	

[a] Secretion was defined if the volume was more than 0 ml (ranging from 0.1 to 20 ml)

[b] Fisher's exact test

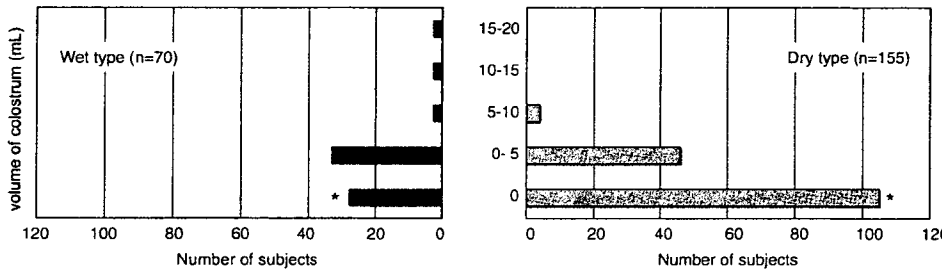

Fig. 1 Distribution of the colostrum secretion volume by earwax type in 70 wet-type women and 155 dry-type women. *Asterisk* represents the frequency of dry-type women without colostrum (105/155) was significantly higher ($P < 0.0002$) than that of wet-type women without colostrum (28/70). Each interval of the colostrum volume includes the right end but not the left end

was significantly higher ($P < 0.0002$, Fisher's exact test) than that of wet-type women without colostrum (28/70 or 40.0%) (Table 1 and Fig. 1). Such a difference was also seen in primipara women without colostrum: 70.5% (55/78) of dry-type women versus 36.7% (11/30) of wet-type women ($P = 0.0019$, Fisher's exact test); and within multipara women without colostrum: 64.9% (50/77) of dry-type women versus 42.5% (17/40) of wet-type women ($P = 0.0297$) (Table 1). Furthermore, the measurable volume of colostrum (average, 1.6 ml) secreted from 50 dry-type women was significantly smaller ($P = 0.0341$, Savage test) than that (average, 4.0 ml) from 42 wet-type women; the 25th, 50th and 75th percentiles of the volume in the dry-type and wet-type women was (0.2, 1.0 and 2.0 ml) and (0.2, 1.1 and 4.0 ml), respectively (Fig. 1).

We have shown that apocrine colostrum secretion from the mammary gland is associated with human earwax-type, leading to an issue that could have very substantial health implications in a wide range of settings from newborn care to cancer etiology. Although several reports suggested a positive association (Petrakis et al. 1975, 1990), our preliminary data denied it (unpublished). Therefore, a role of milk production or lactation initiation in breast cancer remains inconclusive. Endocrine control of lactation develops during pregnancy, and the pituitary gland supplies prolactin and oxytocin as central regulators of apocrine secretion from the mammary gland. Our results suggest that the *ABCC11* gene product (MRP8), an amphipathic anion transporter functioning as an efflux pump (Guo et al. 2003), also plays a role in the colostrum secretion as a peripheral factor independent from the endocrine control. Since there has been no evidence that the colostrum from mothers with dry earwax nourishes their infants less, a role of MRP8 in the colostrum may be confined to its volume. Finally, breast feeding or not, and length of time spent feeding might be associated with colostrum secretion. This could have important implications for anticipatory guidance for mothers planning to breastfeed and based simply on their earwax-type.

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Contraception

Original research article

Effect of placenta previa on blood loss in second-trimester abortion by labor induction using gemeprost

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Abstract

Objectives: The study was conducted to determine whether placenta previa increases bleeding during gemeprost-induced termination of second-trimester pregnancy.

Methods: We carried out a retrospective study of 158 second-trimester terminations between 12 and 21 weeks' gestation. We compared the intraoperative blood loss among three groups: women without placenta previa undergoing gemeprost termination, women with placenta previa undergoing gemeprost termination and women with placenta previa undergoing dilatation and evacuation (D&E).

Results: Eleven of 158 women (7.0%) had placenta previa; four underwent D&E and seven had gemeprost termination. There was no statistical difference in mean intraoperative blood loss among the three groups, although one of the seven women with placenta previa who underwent gemeprost termination developed serious bleeding requiring blood transfusion.

Conclusion: The use of gemeprost for second-trimester pregnancy termination in women with placenta previa seems to be relatively safe and does not increase intraoperative blood loss in the majority of cases.

Keywords: Abortion; Dilatation and evacuation; Gemeprost; Placenta previa; Second trimester

1. Introduction

Placenta previa is one of the most important causes of obstetric hemorrhage [1]. The reported rate of placenta previa at term is approximately 0.5% [2]. Its frequency in the second trimester is significantly higher: approximately 5% at 16 weeks [3,4].

The widespread adoption of fetal screening programs appears to have increased the rate of second-trimester pregnancy terminations in the presence of placenta previa. However, only a few reports have studied the effect of placenta previa on abortion morbidity [5,6]. In most of these reports, dilatation and evacuation (D&E) was used, which is the most common method for second-trimester abortion in the United States [7]. The above reports applied the same procedure to subjects with placenta previa as to those without it, and obtained similar results, that second-trimester pregnancy termination in the presence of placenta previa did not increase bleeding and other forms of maternal morbidity, compared with the outcome of patients without placenta previa.

Prostaglandin analogues are currently the primary alternatives to D&E in labor induction for pregnancy termination in second trimester. Misoprostol is commonly used in the United States [8], while gemeprost is used in Japan. Although uterine perforation occurs far less frequently with labor induction than D&E, labor induction has a greater risk of excessive blood loss [9]. The impact of placenta previa on the technique used for second-trimester termination has been investigated only rarely [10]. In this report, we tested the hypothesis that second-trimester termination by gemeprost is not associated with increased bleeding in patients with placenta previa.

2. Materials and methods

Between January 1994 and January 2006, 178 patients were admitted for termination at 12 to 21 weeks' gestation at Nagasaki University Hospital. The gestational age was

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assessed by the menstrual history and ultrasonographic findings. Pregnancy termination was indicated legally, and written informed consent was obtained from each patient prior to proceeding with treatment.

Just before the termination procedure, all patients were examined by ultrasonography for the presence of placenta previa. Placenta previa was recorded as complete, partial, or low lying. For analysis, we grouped together all the patients with placenta previa. For patients without placenta previa, all abortions were performed after dilating the cervix by laminaria, by the use of gemeprost vaginal pessaries. After removal of laminaria, gemeprost (1 mg) was inserted in the posterior vaginal fornix every 3 h until abortion occurred with a maximum of five gemeprost pessaries over 1 day [9]. On the other hand, for patients with placenta previa, abortions were performed after dilatation of the cervix, either by induction of labor using gemeprost or mechanical evacuation, according to the informed decision of the patient. The uterus was evacuated under general anesthesia using extraction forceps and blunt curettes. Five units of oxytocin or 0.2 mg of methylergometrine maleate was injected intravenously at the completion of the procedure. All patients were treated with prophylactic antibiotics.

We compared the groups with and without placenta previa with regard to patient characteristics. We also compared intraoperative blood loss between patients with and without placenta previa who underwent gemeprost termination, and between patients with placenta previa who underwent gemeprost termination and D&E. Blood loss was quantified by measuring the aspirated amniotic fluid and blood and weighing the gauze used for blood and fluid collection during operation. In our hospital, blood loss is usually recorded in grams because we measure it by weighing the collected fluid in kidney trays or subtracting the weight of dry gauze from that of a blood-soaked one. Since the specific gravity of female blood is approximately 1.053, 1 g is equivalent to 0.95 mL.

Statistical comparison was performed using the two-tailed Student's t test. $p<.05$ was considered significant.

3. Results

We identified 179 patients undergoing second-trimester termination of pregnancy. Of these, 21 were found to be either multifetal pregnancies or lacked documentation about intraoperative blood loss. We analyzed the remaining 158 patients. Table 1 lists the data for patient characteristics and intraoperative blood loss of women with and without placenta previa. Placenta previa was found in 7.0% (11 of 158) of the subjects. There were no significant differences between the two groups with regard to age, parity and gestational age at operation. The mean intraoperative blood loss tended to be larger in the placenta previa group, albeit statistically insignificant (Table 1).

Table 1
Patient characteristics and intraoperative blood loss

	Placenta previa	No placenta previa	p
No. of patients	11 (7.0)	147 (93.0)	NS
Age (years)	28.3±6.8	30.0±6.2	NS
Gravidity	1.3±1.4	1.3±1.4	NS
Parity	0.9±1.1	0.8±2.0	NS
Gestational age (weeks)	16.6±2.7	18.0±2.6	NS
Blood loss (g)	284.1±350	189.6±259	NS

Data are expressed as number (%) or mean±SD. NS, not significant.

Table 2
Characteristics and operative outcome of cases with placenta previa

Case no.	Age	G	P	GA (weeks)	Blood loss (g)	Laminaria	Method
1	31	2	1	17	460	–	Gemeprost
2	27	5	4	19	195	+	Gemeprost
3	21	0	0	14	86	+	Gemeprost
4	41	1	0	18	260	+	Gemeprost
5	17	0	0	16	80	+	Gemeprost
6	28	1	1	19	1272	+	Gemeprost
7	27	1	1	19	60	+	Gemeprost
8	22	1	1	17	330	–	D&E
9	34	0	0	13	142	+	D&E
10	34	1	1	20	140	+	D&E
11	28	2	1	12	100	+	D&E

G, gravida; P, para; GA, gestational age; +, laminaria was used; –, laminaria was not used; method, method used for abortion.

Of the 11 women with placenta previa, labor was induced by gemeprost in seven and D&E in four women (Table 2). The mean intraoperative blood loss for the seven women with placenta previa who underwent termination using gemeprost (344.7 g) was not significantly larger than that of women without placenta previa (189.6 g, $p=.34$) and four women with placenta previa who underwent D&E (178.0 g, $p=.36$).

None of the patients of the two groups bled before, during or after insertion of laminaria. No patient developed uterine rupture, uterine perforation or cervical laceration, and no patient required hysterectomy. Only one woman required blood transfusion because of serious bleeding. She had placenta previa and underwent gemeprost termination (Case 6, Table 2). In this patient, bleeding that developed after the insertion of the first gemeprost pessary was stopped by mechanical evacuation of the uterine content.

4. Discussion

Because it is simple and noninvasive, and does not need any particular skill, labor induction using prostaglandin analogues is becoming increasingly common for second-trimester pregnancy termination. To our knowledge, there is little or no information about the use of this method in the presence of placenta previa. Accordingly, we conducted this retrospective study to determine whether excessive bleeding accompanied second-trimester terminations by gemeprost, the most commonly used agent in Japan, in the presence of placenta previa.

Eleven of 158 (7.0%) women undergoing termination of pregnancy between 12 and 21 weeks had placenta previa.

Seven of the 11 underwent termination using gemeprost. Their mean intraoperative blood loss was 1.8 times greater than that of women without placenta previa, but the difference was statistically insignificant (p=.33).

Blood loss in the seven women who underwent termination by gemeprost was 1.9 times greater than that of four women who underwent D&E, but the difference was also statistically insignificant (Table 2). Although this lack of significance could be due to the small sample size, other reports suggested previously the relative safety of gemeprost for second-trimester termination in women with placenta previa. For example, Thong et al. [9] carried out a retrospective study of 932 second-trimester terminations to determine the efficacy of labor induction by gemeprost. In their study, 80% and 95% of patients aborted within 24 and 48 h, respectively. They did not exclude women with placenta previa from their study group, and overall, only 15 (1.6%) bled more than 500 mL, and 6 (0.6%) required blood transfusion. Significantly, more parous women bled more than 500 mL, but how many of these had placenta previa was not described. After reviewing his experience of 407 second-trimester abortions by labor induction using gemeprost, which comprised approximately 20 placenta previa cases, Deguchi reported that no subjects required laparotomy or blood transfusion because of serious bleeding (K. Deguchi, personal communication, 2005). Considered together, these reports support the notion, although indirectly, that abortion by labor induction using gemeprost during the second trimester is safe and should not be contraindicated even in the presence of placenta previa.

One of seven women in our study developed serious bleeding after the insertion of the first gemeprost pessary, raising the average blood loss of the gemeprost group (Table 2). Although we do not know the details of the case at present, the risk of bleeding should be borne in mind when performing gemeprost termination. That no method other than rapid evacuation of the uterine contents is effective for hemostasis underscores the importance of adequate dilatation of the cervix by laminaria.

Ruano et al. [10] reported that in the presence of placenta previa, second- and third-trimester termination of pregnancy by labor induction carried a substantial risk of hemorrhage. Of the 15 women in their study with complete placenta previa at an average of 22.4 (18–33) weeks' gestation who underwent labor induction including two by gemeprost, four required blood transfusions and one required hysterectomy. They also suggested that feticide before inducing labor might reduce maternal blood loss.

Although our preliminary results lacked statistical power, they show that second-trimester termination by gemeprost was not associated with excessive bleeding in the majority of cases with placenta previa. Intraoperative blood loss in patients with placenta previa varied considerably for unknown reasons. Future work should further examine the effect of gestational age, precise location of the placenta, history of previous cesarean section, presence of placenta accreta or uterine myoma and other factors on blood loss after labor induction by gemeprost for second-trimester termination. Such studies will facilitate identification of women with placenta previa at risk for excessive bleeding in gemeprost-induced second-trimester termination.

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