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ORIGINAL ARTICLE

Effect of epidural analgesia on cervical ripening using dinoprostone vaginal inserts

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Abstract

Objective To clarify whether the duration from cervical ripening induction to labor onset is prolonged when epidural analgesia is administered following application of dinoprostone vaginal inserts vs. cervical ripening balloon.

Methods This retrospective study included mothers with singleton deliveries at a single center between 2020–2021. Nulliparous women who underwent labor induction and requested epidural analgesia during labor after 37 weeks of gestation were included. The duration from cervical ripening induction to labor onset was compared between women using a dinoprostone vaginal insert and those using a cervical ripening balloon and between women who received epidural analgesia before and after labor onset.

Results In the dinoprostone vaginal insert group, the duration was significantly shorter in the subgroup that received epidural analgesia after labor onset (estimated median, 545 [95% confidence interval: 229–861 min]) than the subgroup that received it before labor onset (estimated median, 1,570 [95% confidence interval: 1,226–1,914] min, p = 0.004). However, in the cervical ripening balloon group, the difference between subgroups was not significant. The length of labor among the groups was also not significantly different.

Conclusion Epidural analgesia as labor relaxant adversely affected the progression of uterine cervical ripening when dinoprostone vaginal inserts were used, whereas it did not affect cervical ripening when a mechanical cervical dilatation balloon was used. The present results are significant for choosing the appropriate ripening method.

Keywords Cervical ripening · Dinoprostone vaginal inserts · Labor induction · Epidural analgesia · Prostaglandin E2

Introduction

The use of epidural analgesia with labor relaxants would more likely require oxytocin augmentation and a longer labor duration [1–5]. Autonomic imbalance has been proposed as the reason for the association between epidural analgesia and prolonged labor [6, 7]. While administering epidural analgesia during labor results in relaxation in women undergoing delivery, its side effects are often challenging to manage during delivery.

Cervical ripening is a common procedure that is attempted before labor induction to ensure efficient labor progression [8, 9]. It can be performed using a mechanical dilator, balloon, or dinoprostone vaginal inserts (prostaglandin E2 [PGE2]). Although PGE2 vaginal inserts directly promote cervical ripening while also indirectly promoting uterine contractions, we hypothesized that induction of uterine contractions with PGE2 may also be effective for the progression of labor. In fact, in our previous report, PGE2 vaginal inserts often induced spontaneous labor [10]. Therefore, we suppose that the suppression of uterine contractions by epidural analgesia administration when using PGE2 vaginal inserts may counteract cervical ripening.

The aim of the present study was to clarify whether using PGE2 vaginal inserts for cervical ripening prolongs the duration from cervical ripening to labor onset when epidural

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analgesia is administered compared to that when cervical ripening is induced using a mechanical method.

Materials and Methods

This retrospective study included participants who underwent singleton deliveries at the St. Marianna University Hospital between 2020–2021. Nulliparous women who underwent induced labor and requested epidural analgesia after 37 weeks of gestation were included in this study. Cases of fetal death, pregnant women who received on-demand anesthesia during labor, or premature rupture of the membranes were excluded.

Characteristics of pregnant women and infants as well as information about the delivery course and time were retrieved from medical records. As the primary outcome, the duration from cervical ripening induction to the onset of labor was compared between pregnant women who received epidural analgesia for relaxant labor after labor onset and those who used it before labor onset.

In the present study, onset of labor was defined as the presence of regular painful contractions for less than 10 min or more than 6 times per hour that results in delivery, according to the Glossary of Obstetrics and Gynecology Terms published by the Japan Society of Obstetrics and Gynecology [11]. This definition does not include findings of the uterine os, such as dilatation, effacement, and location of the fetal presenting part on internal examination.

Cervical ripening procedure

Cervical ripening was attempted at our hospital when the Bishop score was ≤ 6 points. A cervical ripening balloon (Mini Metro®, Muranaka Medical Instruments Co. LTD, Japan) was used in 2020 when pharmacological cervical ripening methods were not available in Japan. PGE2 vaginal inserts (PROPESS® 10 mg, Ferring Pharmaceuticals, Switzerland) were used after 2021.

a. Cervical ripening balloon

The following protocol was followed for cervical ripening using Mini Metro®: Cardiotocography was performed prior to insertion. A cervical ripening balloon was inserted and inflated with 40 mL water at 5 pm on the day before labor was to be induced. Intermittent cardiotocographic monitoring was performed after balloon insertion.

b. PGE2 vaginal inserts

PROPESS (10 mg) was used as a cervical ripening agent according to the manufacturer's instructions. Continuous cardiotocographic monitoring was performed before applying the PGE2 vaginal insert. PGE2 was applied at 8 am on the day when labor was to be induced. Pelvic examination was performed at 3, 6, 9, and 12 h after application. If any of the following events occurred, the PGE2 vaginal insert was promptly removed: rupture of the membranes, tachysystole or tetanic contraction, signs of non-reassuring fetal status, or systemic signs such as nausea, vomiting, and hypotension. Twelve hours after application, the PGE2 vaginal insert was removed regardless of the presence or absence of cervical ripening.

Methods of epidural analgesia

Epidural analgesia was administered upon patients' request upon experiencing unbearable pain, regardless of the progression of cervical dilatation and contractions. The epidural space was identified by loss of resistance to air at the L3–L4 (L2–L3; L4-L5) interspace, and an epidural catheter was advanced 3.0–5.0 cm into the epidural space. An analgesic mixture of 4 mL of 0.1% ropivacaine with 2 mcg fentanyl was administered as a bolus dose on-demand using a patient-controlled epidural analgesia pump (lockout time, 15 min).

Ethics statement

This study was approved by the ethics board of the St. Marianna University School of Medicine, Kawasaki, Japan (No. 5575; 2022). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Statistical analysis

Statistical significance was defined as a p-value < 0.05. Data were analyzed using Statistical Package for Social Sciences for Windows version 25.0 (IBM, Armonk, NY, USA). Continuous variables were compared using the Mann–Whitney U test for nonparametric data. Categorical variables are reported as percentages and were compared using Fisher's exact test. The cumulative probability of the duration from cervical ripening induction to onset of labor was estimated using the Kaplan–Meier method. Onset of labor was considered as the "event," while emergency Cesarean section was considered as the "censor." Survival curves were compared using log-rank tests.

Results

Overall, there were 1,280 cases of singleton deliveries at our hospital during the study period. Of these, epidural analgesia was administered during labor and after 37 weeks of gestation in 334 cases. After excluding 122 cases of multiparous women and a pregnant woman with fetal death and 162 participants who received on-demand anesthesia during labor and had premature rupture of membranes, 49 participants

who underwent labor induction with epidural analgesia administration were analyzed (Fig. 1).

Participants were divided into two groups based on the use of analgesia before and after labor onset. The demographics of the participants are shown in Table 1**.** The number of participants who received analgesia before and after the onset of labor was 20 and 29, respectively. There were no differences in patient characteristics between the two groups.

The duration from cervical ripening induction using a cervical ripening balloon or a PGE2 vaginal insert to the onset of labor stratified by the administration of epidural analgesia before and after labor onset is presented in Fig. 2. The duration was significantly shorter in women who received epidural analgesia after the onset of labor (estimated median, 765 [95% confidence interval: 484–1,046] min) than in women who received it before the onset of labor (estimated median, 1,585 [95% confidence interval: 1,210–1,960] min), p = 0.002.

The duration from cervical ripening induction to the onset of labor stratified by epidural analgesia administration before and after labor onset in women who received a cervical ripening balloon or a PGE2 vaginal insert is presented in Fig. 3. In the PGE2 vaginal insert group, the duration was significantly shorter in the subgroup that

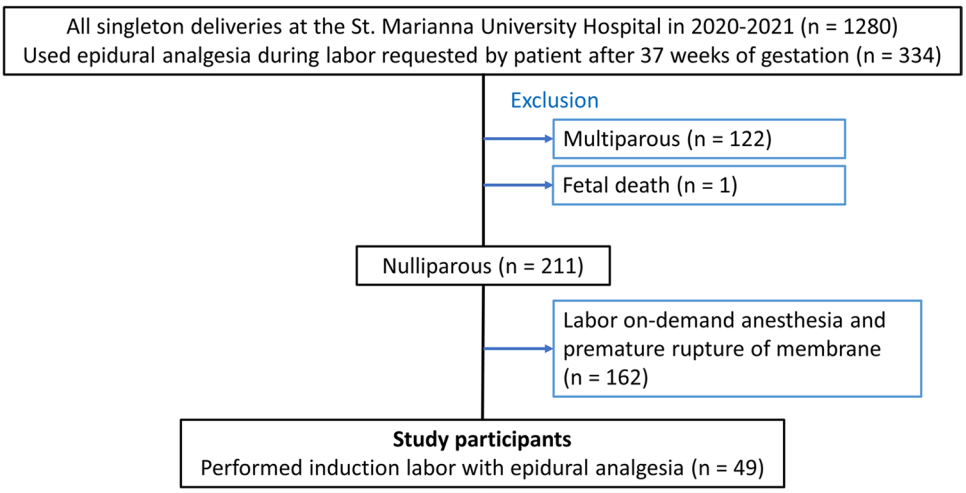

Fig. 1 Study flow diagram

Table 1 Demographics of study participants

	Used analgesia before onset of labor (n = 20)	after onset of labor (n = 29)	p-value
Maternal age (years)	38 (28–42)	35 (26–41)	ns
Maternal height (cm)	157 (146–169)	160 (148–173)	ns
Weight at pregnancy (kg)	51 (43–82)	54 (41–83)	ns
Gravida	0 (0–1)	0 (0–4)	ns
Indication of induction of labor			
Over due date	14 (70%)	22 (76%)	ns
Pre-eclampsia	4 (20%)	3 (10%)	ns
Others	2 (10%)	3 (10%)	ns
Gestational week at delivery	40 (39–41)	40 (36–41)	ns
Instrumental delivery	7 (35%)	9 (31%)	ns
Cesarean section	6 (30%)	3 (10%)	ns
Neonatal weight (g)	3,117 (2,684–3,800)	3,232 (2,138–3,852)	ns
Apgar score 1 min	8 (1–9)	8 (5–10)	ns
Apgar score 5 min	9 (2–10)	9 (9–10)	ns
Umbilical arterial pH	7.36 (7.07–7.43)	7.36 (7.01–7.44)	ns
Amount of bleeding at delivery (g)	585 (275–2,421)	669 (152–1,753)	ns

†Data indicate n (%) or median (range)

‡ ns: not significant

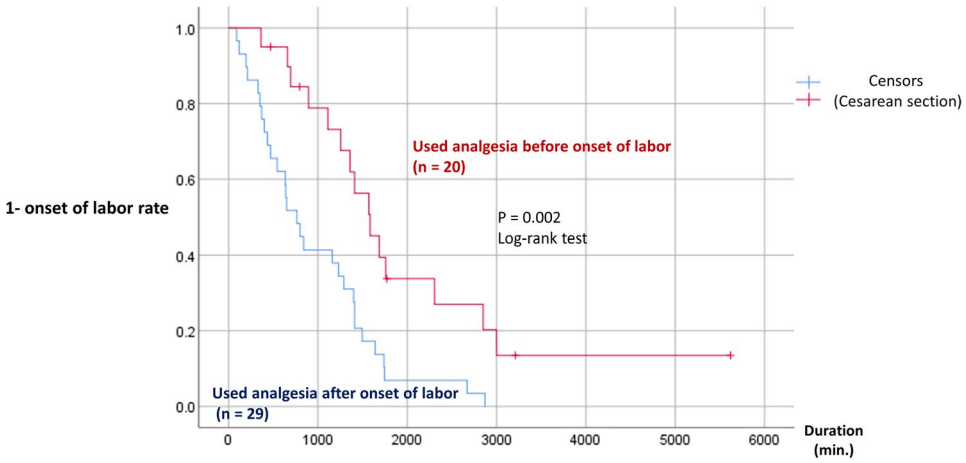

Fig. 2 Duration from the induction of cervical ripening using a cervical ripening balloon and dinoprostone vaginal inserts to the onset of labor

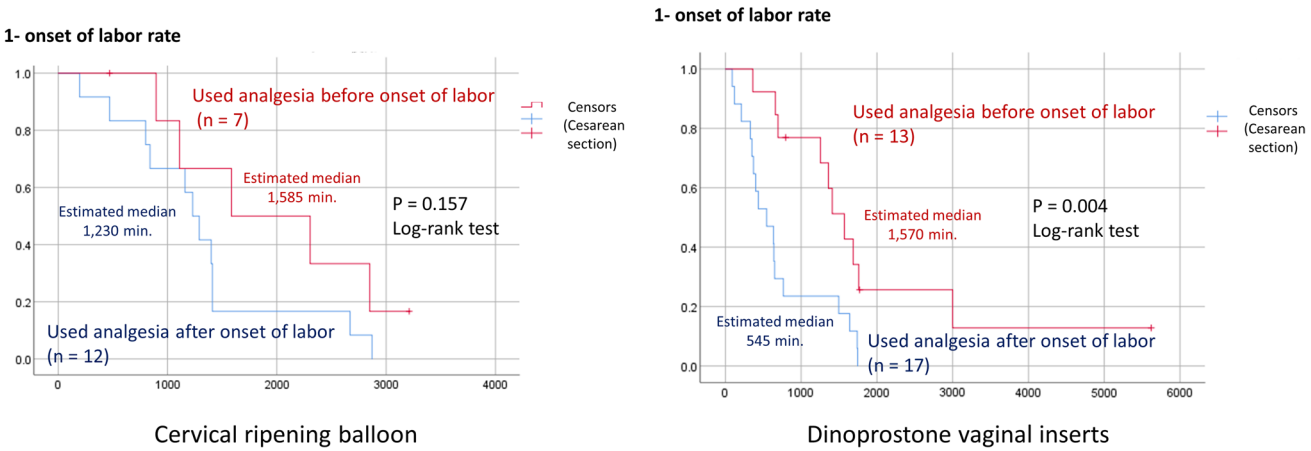

Fig. 3 Duration from the induction of cervical ripening to the onset of labor using a cervical ripening balloon and dinoprostone vaginal inserts

received epidural analgesia after the onset of labor (estimated median, 545 [95% confidence interval: 229–861] min) than in the subgroup that received it before the onset of labor (estimated median, 1,570 [(95% confidence interval: 1,226–1,914] min), p = 0.004. However, in the cervical ripening balloon group, the difference between subgroups was not significant.

The duration from cervical ripening induction to the onset of labor and labor length stratified by the cervical ripening method is presented in Table 2**.** The number of women who received analgesia before the onset of labor was 7 (37%) in the cervical ripening balloon group and 13 (43%) in the PGE2 vaginal insert group. Two (11%) and three (10%) women who received a balloon and a PGE2 insert, respectively, underwent Cesarean section. Eight (42%) and 12 (40%) women who received a balloon and a PGE2 insert, respectively, experienced rupture of membranes. Meanwhile, the length of labor among these groups was not significantly different.

Discussion

Our results suggest that epidural analgesia as labor relaxant adversely affects the progression of uterine cervical ripening when PGE2 vaginal inserts are used, whereas it does not adversely affect cervical ripening when a mechanical cervical dilatation balloon is used.

Cervical ripening induces labor because of the positive feedback between uterine cervical dilatation and oxytocin secretion, which induces uterine contractions. Thus, the use of uterotonic drugs is recommended after cervical ripening to avoid uterine trauma and/or a non-reassuring fetal status [12].

A meta-analysis comparing the balloon and PGE2 cervical ripening methods demonstrated no differences in terms of vaginal delivery within 24 h or the incidence of Cesarean delivery [13]. However, comparative studies on the use of cervical-ripening balloons and PGE2 vaginal

Table 2 Duration from administration of cervical ripening to onset of labor and labor length stratified by methods

		Cervical ripening method			
		Balloon		Dinoprostone vaginal inserts	
		N = 19		N = 30	
Duration from administration of cervical ripening to onset of labor					
Epidural analgesia					
	before onset of labor	(n = 7)	1,585 (151–3,019)	(n = 13)	1,570 (1,226–1,914) min
	after onset of labor	(n = 12)	1,230 (1,009–1,450)	(n = 17)	**545 (229–861)*** min
Duration the first stage of labor					
Epidural analgesia					
	before onset of labor	(n = 7)	304 (121–487)	(n = 13)	256 (195–317) min
	after onset of labor	(n = 12)	345 (213–477)	(n = 17)	210 (176–244) min
Duration of the second stage of labor					
Epidural analgesia					
	before onset of labor	(n = 7)	73 (3–143)	(n = 13)	98 (0–244) min
	after onset of labor	(n = 12)	86 (39–133)	(n = 17)	112 (58–166) min
Total duration of labor					
Epidural analgesia					
	before onset of labor	(n = 7)	375 (263–487)	(n = 13)	465 (194–736) min
	after onset of labor	(n = 12)	422 (265–579)	(n = 17)	437 (293–581) min

†Data indicate the estimated median time (95% confidence interval) using the Kaplan–Meier method

*$p < 0.05$ compared to group of before onset of labor

inserts have demonstrated not only a low oxytocin augmentation rate but also a high rate of uterine contractions and umbilical arterial blood pH < 7.1 in cases receiving PGE2 [13–15]. In this study, we compared the time required for complete cervical ripening between the two methods as the primary outcome, revealing that epidural analgesia can prolong the time required for cervical ripening particularly when PGE2 vaginal inserts are used. This may be because epidural analgesia suppresses the cervical ripening effect of uterine contractions.

Natural PGE2 is locally produced by the amniotic membrane during labor, and it ripens the cervix and induces uterine contractions [16]. Local effects of PGE2 around the uterine cervix include changes in cervical consistency, dilation, and effacement [17]. Additionally, PGE2 modulates inflammatory processes that occur with cervical ripening [17, 18]. PGE2 also induces uterine contractions, including stimulating endogenous prostaglandin $F_{2\alpha}$ production and sensitizing the myometrium to the effects of endogenous or exogenous oxytocin [17]. There are four subtypes of PGE2 receptors: EP1, EP2, EP3, and EP4 [19]. The number of receptors, particularly EP2, is increased in pregnancy and then decreases at term and before the onset of labor [20]. Meanwhile, EP1 and EP3 are mainly responsible for uterine contractions, and EP4 is responsible for cervical ripening [19]. Although PGE2 receptors are less abundant and have a weaker effect on uterine contraction in uterine smooth muscles, they act on the upper uterine muscles for uterine contraction via EP1 and EP3 as well as on the lower uterine muscles for uterine relaxation and cervical ripening via EP2 and EP4 [19].

It is thought that cervical administration of PGE2 exerts a stronger cervical ripening effect. Furthermore, as PGE2 also induces uterine contractions, uterine contractions in addition to direct cervical ripening are thought to promote more effective cervical ripening. A previous study that compared the use of oral dinoprostone and vaginal PGE2 for labor induction in multiparous women at term demonstrated that the rate of successful vaginal delivery was significantly higher in the vaginal group (72%) than in the oral dinoprostone group (35%), and that the proportion of cases requiring predelivery oxytocin in the vaginal group was significantly lower than that in the oral dinoprostone group (24% vs. 57%) [21]. PGE2 produces a biphasic effect on the myometrium, resulting in initial contraction followed by relaxation [19]. Thus, the results of previous studies and those of our study are plausible.

Our results also demonstrated that the lengths of the first and second stages of labor and the overall duration of labor did not differ, regardless of the cervical ripening method and timing of epidural analgesia administration. We believe that the effects of the timing of epidural analgesia administration on labor duration after the onset of labor are limited. A prolonged latent phase is associated with several clinical features, including deficient pre-labor cervical remodeling, excessive sedation, analgesia or anesthesia, maternal obesity, malposition, chorioamnionitis, and post-term labor, some of which can also cause active-phase abnormalities [22–24]. The latent phase can be prolonged by administering epidural analgesia early in labor. However, as neuraxial anesthetic agents and techniques have changed substantially, early administration of epidural analgesia using agents with negligible motor blockade might have very few adverse effects on the overall duration of labor [22, 25, 26]. According to a recent review, the mechanism by which epidural drugs alter the latent phase remains unknown. It may be associated with altered contractility; furthermore, it might be influenced by the autonomic blockade provided by the neuraxial block [22]. Our results of a prolonged effect observed only in cases that received PGE2 may support the mechanism of progression by contractility in the latent phase.

The limitations of the present study include its retrospective nature, lack of randomization, and a small number of patients. Furthermore, various factors related to anesthesia, such as the amount of local anesthetic agent and the assessment of the analgesic range, were not compared, although these factors can also affect labor progression. However, to our knowledge, this is the first clinical study to determine whether PGE2 vaginal inserts are suitable for pregnant women who are to be administered with epidural analgesia during labor. As even PGE2 vaginal inserts induce uterine contractions, cervical balloons are occasionally a better choice for pregnant women who require early analgesia administration for efficient cervical dilatation.

In conclusion, our results suggest that epidural analgesia as labor relaxant adversely affects the progression of uterine cervical ripening when PGE2 vaginal inserts are used. However, epidural analgesia did not adversely affect cervical ripening when a mechanical cervical dilatation balloon was used. The present results are significant for choosing the appropriate ripening method.

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Author Contributions JH and CH conceived the study, wrote the initial protocol, and analyzed the data. JH wrote the first draft of the manuscript. JH, CH, SS and NF collected and analyzed the data. JH and CH coordinated the study and created the database. JH performed the statistical analyses. All authors contributed to the writing of the manuscript. JH and MS is the guarantor for the study. All authors had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.. All the authors contributed significantly to this work.

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Data availability Data sharing not applicable – no new data generated.

Declarations

Conflict of interest The authors declare no competing interests in association with the present study.

References

1. Sharma SK, McIntire DD, Wiley J, Leveno KJ. Labor analgesia and cesarean delivery: an individual patient meta-analysis of nulliparous women. Anesthesiology 2004;100:142–8; discussion 6A
2. Liu EH, Sia AT. Rates of caesarean section and instrumental vaginal delivery in nulliparous women after low concentration epidural infusions or opioid analgesia: systematic review. BMJ. 2004;328:1410.
3. Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. Am J Obstet Gynecol. 2002;186:S69-77.
4. Lieberman E, Davidson K, Lee-Parritz A, Shearer E. Changes in fetal position during labor and their association with epidural analgesia. Obstet Gynecol. 2005;105:974–82.
5. Shields SG, Ratcliffe SD, Fontaine P, Leeman L. Dystocia in nulliparous women. Am Fam Physician. 2007;75:1671–8.
6. Leighton BL, Halpern SH, Wilson DB. Lumbar sympathetic blocks speed early and second stage induced labor in nulliparous women. Anesthesiology. 1999;90:1039–46.
7. Wong CA, Scavone BM, Peaceman AM, McCarthy RJ, Sullivan JT, Diaz NT, et al. The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. N Engl J Med 2005;352:655-65
8. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009;114:386-97
9. Penfield CA, Wing DA. Labor induction techniques: which is the best? Obstet Gynecol Clin North Am. 2017;44:567–82.
10. Furuya N, Hasegawa J, Saji S, Homma C, Nishimura Y, Suzuki N. Optimal cervical-ripening method for labor induction in Japan after the era of controlled-release dinoprostone vaginal insert. J Obstet Gynaecol Res 2023;50:140–46
11. Gynecology JSoOa, editor. Glossary of obstetrics and gynecology Terms. 4th ed. Tokyo: Kyorin-sha; 2018.
12. Tenore JL. Methods for cervical ripening and induction of labor. Am Fam Physician. 2003;67:2123–8.
13. Liu YR, Pu CX, Wang XY, Wang XY. Double-balloon catheter versus dinoprostone insert for labour induction: a meta-analysis. Arch Gynecol Obstet. 2019;299:7–12.
14. Jozwiak M, Oude Rengerink K, Ten Eikelder ML, van Pampus MG, Dijksterhuis MG, de Graaf IM, et al. Foley catheter or prostaglandin E2 inserts for induction of labour at term: an open-label randomized controlled trial (PROBAAT-P trial) and systematic review of literature. Eur J Obstet Gynecol Reprod Biol 2013;170:137–45
15. Cromi A, Ghezzi F, Uccella S, Agosti M, Serati M, Marchitelli G, Bolis P. A randomized trial of preinduction cervical ripening: dinoprostone vaginal insert versus double-balloon catheter. Am J Obstet Gynecol. 2012;207(125):e1-7.

16. Thomas J, Fairclough A, Kavanagh J, Kelly AJ. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. Cochrane Database Syst Rev 2014;2014:CD003101.
17. Shirley M. Dinoprostone Vaginal insert: a review in cervical ripening. Drugs 2018;78:1615–24
18. Bakker R, Pierce S, Myers D. The role of prostaglandins E1 and E2, dinoprostone, and misoprostol in cervical ripening and the induction of labor: a mechanistic approach. Arch Gynecol Obstet. 2017;296:167–79.
19. Li WJ, Lu JW, Zhang CY, Wang WS, Ying H, Myatt L, Sun K. PGE2 vs PGF2alpha in human parturition. Placenta. 2021;104:208–19.
20. Smith GC, Wu WX, Nathanielsz PW. Effects of gestational age and labor on the expression of prostanoid receptor genes in pregnant baboon cervix. Prostaglandins Other Lipid Mediat. 2001;63:153–63.
21. Yokoyama N, Suzuki S. Comparison of obstetric outcomes between controlled-release dinoprostone vaginal delivery system (PROPESS) and administration of oral dinoprostone for labor induction in multiparous women at term. Cureus. 2023;15:e40907.
22. Cohen WR, Friedman EA. The latent phase of labor. Am J Obstet Gynecol. 2023;228:S1017–24.
23. Polonia Valente R, Santos P, Ferraz T, Montenegro N, Rodrigues T. Effect of obesity on labor duration among nulliparous women with epidural analgesia. J Matern Fetal Neonatal Med. 2020;33:2195–201.
24. Tilden EL, Phillippi JC, Ahlberg M, King TL, Dissanayake M, Lee CS, Snowden JM, et al. Describing latent phase duration and associated characteristics among 1281 low-risk women in spontaneous labor. Birth 2019;46:592–601
25. Chen S, Ye S, Wu C, Jia X, Li S, Zeng X. Effects of epidural analgesia at 1 cm cervical dilatation on labor interventions in full-term primigravida: a retrospective cohort study. J Obstet Gynaecol Res. 2023;49:1545–50.
26. Shiro M, Nakahata K, Minami S, Kawamata T, Ino K. Perinatal outcome of vaginal delivery with epidural analgesia initiated at the early or late phase of labor period: a retrospective cohort study in the Japanese population. J Obstet Gynaecol Res. 2018;44:1415–23.