ORIGINAL ARTICLE

Efficacy of Vaginal Progesterone for Maintenance Therapy after Arrested Preterm Labor: A Randomized Controlled Trial

Raksina Nuprom, MD[1], Pakprapa Chaipakdi, MD[1]

[1] Department of Obstetrics and Gynecology, Hatyai Hospital, Hat Yai, Songkhla, Thailand

Objective: To evaluate whether 400 milligrams of vaginal progesterone, as a maintenance tocolysis, could prolong the latency to delivery, prevent preterm birth, reduce adverse neonatal outcomes, and delay cervix shortening after arrested preterm labor.

Materials and Methods: An open-label randomized controlled trial was conducted on 80 singleton pregnant women with symptomatic preterm labor, who were successfully arrested with Nifedipine as acute tocolysis, at gestational ages 24 to 33 weeks and 6 days, at Hatyai Hospital. Participants were then randomly allocated using a permuted block of four to either the vaginal progesterone group or the control group.

Results: The vaginal progesterone group resulted in a longer mean latency to delivery at 47.3±17.1 versus 34.2±18.1 days (p<0.001), a lower preterm birth rate at 12.5% versus 35.0% (p=0.036), a higher gestational age at delivery of 38.5±1.3 versus 36.7±2.5 weeks (p<0.001), and improved birth weight of 2,932.6±309.9 versus 2,627.1±517.3 grams (p=0.002). There were no significant differences in the delay of cervical shortening at –3.2±2.8 versus –4.7±5.0 mm (p=0.192) or the rate of neonatal intensive care unit (NICU) admission of 4% versus 11% (p=0.086) or the rate of birth asphyxia of 5% versus 10% (p=0.675).

Conclusion: Administering 400 milligrams of vaginal progesterone as a maintenance tocolysis in arrested preterm labor effectively prolongs latency to delivery, reduces the rate of preterm birth, and improves birth weight. However, it fails to delay cervical shortening and does not decrease the rate of NICU admission or occurrence of birth asphyxia.

Keywords: Arrested preterm labor; Preterm birth; Vaginal progesterone; Maintenance therapy

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Spontaneous preterm labor typically stands as the leading cause of preterm births, presenting significant challenges due to its potential for severe impacts on the developing fetus. Globally, approximately 15 million preterm births occur each year, constituting 1 in 10 births. Tragically, over 1 million infants succumb annually due to complications stemming from preterm birth. Surviving premature infants often confront enduring hurdles, including visual and auditory impairments, as well as developmental setbacks[1].

According to statistical data from Hatyai Hospital, the years 2020 and 2021 saw respective preterm labor rates of 8.2% and 7.3% among patients seeking treatment in the labor room. More than half of the patients presenting with threatened preterm labor and preterm labor faced recurrent episodes of preterm labor. In 2022, the incidence of preterm births exceeded 8.32%, a figure significantly higher than the incidence of other pregnancy related issues. Therefore, preventing and mitigating preterm birth remains a significant challenge in obstetric care.

Progesterone plays a crucial role in maintaining uterine quiescence. Toward the end of pregnancy, progesterone withdrawal is considered a parturition-triggering event, leading to studies that aim to find the benefits of progesterone in preventing preterm labor[2].

Women experiencing preterm labor often encounter recurring episodes of preterm labor even after successful suppression with acute tocolysis, potentially resulting in preterm birth. The benefits of vaginal progesterone as maintenance tocolysis remain controversial, but there is a suggestion of its potential effectiveness in preventing preterm labor. The dosage

Correspondence to:

Nuprom R.

Department of Obstetrics and Gynecology, Hatyai Hospital, Hat Yai, Songkhla 90110, Thailand.

Phone: +66-86-9577836

Email: raksina.nup@gmail.com

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of vaginal progesterone used for preventing preterm labor is also a subject of ongoing debate, as shown in meta-analysis studies[3].

Studies have suggested that a 200-milligram dose of vaginal progesterone is ineffective as a maintenance tocolysis for preventing preterm labor[4-8]. In a 1985 study on hormonal concentrations during pregnancy in humans conducted by Pasqualini and Kincl[9], a decrease of approximately 6 ng/mL in maternal peripheral plasma progesterone levels 4 to 5 days prior to parturition is considered a parturition-triggering event associated with the progression of labor. However, the administration of 200 milligrams of micronized progesterone vaginally results in absorption to a maximal plasma concentration ranging from 4 to 12 ng/mL[10]. This level may be insufficient to maintain the required plasma progesterone levels and prevent preterm labor in the second to third trimesters of pregnancy.

Studies have suggested that a higher dosage of vaginal progesterone, specifically 400 milligrams, demonstrates a positive effect in preventing preterm birth as a maintenance tocolysis[11-14]. Despite limited research on the maximal plasma concentration of progesterone after the vaginal administration of 400 milligrams of micronized progesterone, there is a possibility of its efficacy in preventing preterm labor due to the higher plasma levels of progesterone.

When considering the route of administration for micronized progesterone, studies have explored the efficacy and adverse effects of both vaginal and oral administration. The findings suggest that the vaginal route is preferable due to its lower incidence of undesirable side effects, including sleepiness, fatigue, and headaches. Moreover, the vaginal route offers enhanced bioavailability compared to the oral route[15-17].

In Thailand, limited research has been conducted on the efficacy of vaginal progesterone as a maintenance tocolysis and its capacity to delay cervical shortening. Therefore, the objective of the present study was to assess whether a dosage of 400 milligrams of vaginal progesterone could extend the latency to delivery, prevent preterm birth, reduce adverse neonatal outcomes, and delay cervical shortening following arrested preterm labor.

Materials and Methods

The present study collected participant data between November 2022 and August 2023 at Hatyai Hospital in Songkhla, Thailand. It was approved by the Ethics Committee for Research in Human Subjects at Hatyai Hospital (IRB: HYH-EC 079-65-01) on November 19, 2022, and was registered with the Thai Clinical Trials Registry (TCTR) under the registration ID: TCTR20230901006.

An open-label randomized controlled trial was conducted on 80 singleton pregnant women with gestational ages ranging from 24 weeks to 33 weeks and 6 days, who presented with intact membranes and symptomatic preterm labor. In the present study, symptomatic preterm labor consisted of two categories, threatened preterm labor, defined as regular uterine contractions (one in 10 minutes) detected by cardiotocography persisting after at least one hour of rest, with contraction forces reaching a minimum of 150 Montevideo units in a 10-minute span, capable of initiating the progression of labor, without cervical change[18-21]; and established preterm labor, defined as regular uterine contractions (four contractions in 20 minutes) accompanied by a change in cervical dilatation, effacement, or both. It could also be characterized by the initial presentation with regular uterine contractions (four contractions in 20 minutes) and cervical dilatation of at least 2 cm[22].

Exclusion criteria included multifetal gestations, placenta previa or abruption, cervical os opening greater than 4 centimeters, a history of cervical cerclage, and a history of vaginal progesterone use for other indications. Additionally, individuals with contraindications for oral acute-phase tocolysis (Nifedipine)[22], such as lethal fetal anomalies, intrauterine fetal demise, non-reassuring fetal status, preeclampsia, unstable maternal vital signs, chorioamnionitis, or allergic reactions to Nifedipine had also been excluded from the study.

Eligible participants that underwent standard preterm labor inhibition using oral acute-phase tocolysis according to the Hatyai Hospital protocol. Those facing threatened preterm labor receive the same acute-phase tocolytic agents as participants with established preterm labor. The treatment protocol involved an initial loading dose of 20 milligrams of Nifedipine administered every 30 minutes for two doses, followed by 20 milligrams of Nifedipine given at 6 to 8 hours intervals over 48 hours[23]. Furthermore, each participant received four doses of 6 milligrams of intramuscular Dexamethasone to promote fetal lung maturation[23]. Eligible participants with arrested preterm labor were provided with a written informed consent form that included research details and contact information.

Participants with arrested preterm labor, defined as the absence of uterine contractions for at least 12

hours, who consented to participate in the present study were then randomly allocated to either the vaginal progesterone group or the control group using a pre-generated permuted block of four, concealed within an opaque envelope to ensure the investigator remained blinded. Prior to allocation, a pelvic examination was performed to assess cervical dilatation, effacement, and consistency. Transabdominal ultrasound was conducted to estimate fetal weight, fetal presentation, placental location, and amniotic fluid index, while transvaginal ultrasound was performed to assess the initial cervical length by the first sonographer. A transvaginal probe was positioned within the anterior fornix of the vagina when the maternal bladder was empty. Subsequently, the cervical length measurement was determined by selecting the shortest measurement from three readings obtained using calipers placed at the internal os and external os[24]. The first sonographer collected clinical data from the participants before allocation, as part of the blinding process.

After successfully arresting preterm labor, the vaginal progesterone group received 400 milligrams of micronized progesterone (Utrogestan® 100 mg), administered as four capsules, in the form of vaginal suppositories once daily. This treatment continued until participants reached a gestational age of 37 weeks or until delivery if it occurred before 37 weeks. The micronized progesterone, prepared by a pharmacist, was dispensed in envelopes, with the number of capsules corresponding to the days until the subsequent visit. In contrast, the control group solely underwent observation. Participants in the vaginal progesterone group were taught how to use the medication according to Besins healthcare instructions for medical usage[25].

Antenatal care (ANC) visits were scheduled for both groups seven to ten days after enrollment to evaluate transvaginal cervical length (TVCL). This assessment was conducted by a second sonographer who remained blinded to the treatment each patient received and had no access to the initial TVCL recorded at enrollment. Both sonographers were trained by a board-certified Maternal-Fetal Medicine specialist before the trial began, and it was confirmed that the differences in their measurement results were less than 10% to minimize interobserver variation. Subsequently, participants were monitored at 2- to 3-week intervals until delivery to assess their adherence to the protocol by counting the remaining capsules. The difficulties in using vaginal progesterone and satisfaction with the treatment were assessed during ANC visits through yes-or-no questions. Data on obstetric and neonatal outcomes were obtained from the medical records of Hatyai Hospital. To minimize confounding factors, the present study excluded cases of indicated preterm delivery, including conditions such as preeclampsia and non-reassuring fetal status. The primary outcome measure was the latency to delivery, which was the time from the onset of symptomatic preterm labor until delivery. The secondary outcomes included the preterm birth rate, gestational age at delivery, adverse neonatal outcomes such as low birth weight, defined as 1,500 to 2,500 grams[23], neonatal intensive care unit (NICU) admission, birth asphyxia defined as an Apgar score lower than 7 at 1 and 5 minutes[26], and mean differences in cervical length between the first and second TVCL measurements.

The sample size calculation, utilizing the formula for comparing two independent means, was based on a previous study conducted by Borna and Sahabi in 2008[11]. In their research, they compared the mean latency to delivery between the vaginal progesterone group (36.1±17.9 days) and the control group (24.5±27.2 days) to achieve a statistical power of 80% and a significance level of 5%. The calculated sample size was 76, augmented by 15% to account for dropout cases, resulting in a total of 90 cases.

Data analysis and processing were conducted using R software, version 4.2.1. The presentation of fundamental data involved displaying continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR), while discrete variables were presented as counts and percentages. To compare continuous variables between the two groups, an initial assessment of the data distribution was performed through the Shapiro-Wilk normality test at a significance level of 0.05. This procedure preceded the selection of either Student's t-test or the Wilcoxon rank-sum test for further analysis. Furthermore, a comparison of discrete variables between the two groups was carried out using either Pearson's chi-squared test or Fisher's exact test. Univariate analysis was used to evaluate the relative risk, along with a 95% confidence interval (CI).

Results

Ninety eligible women with arrested preterm labor were recruited for the present study. However, six individuals declined to participate, resulting in a final cohort of 84 eligible participants. Among these participants, 42 were assigned to the vaginal progesterone group, while the remaining 42 were

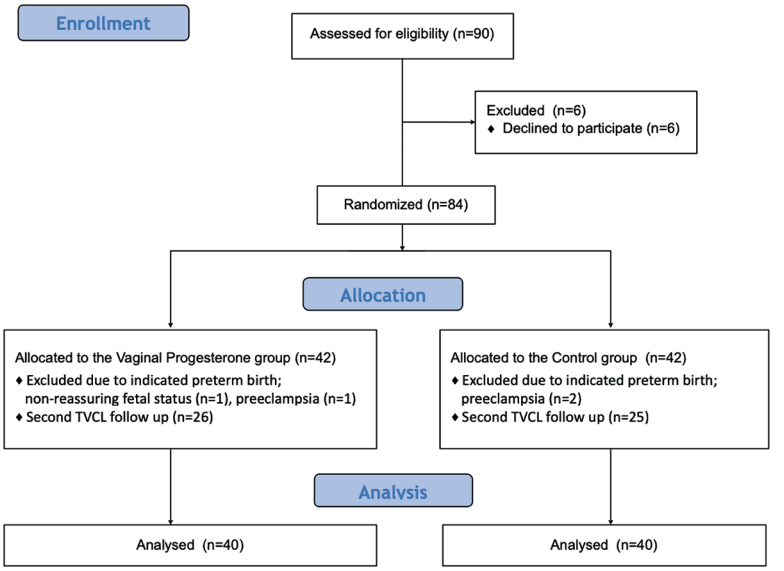

Figure 1. Trial profile - CONSORT flow diagram.

Table 1. Obstetrical and clinical data between groups

Characteristics	Total (n=80)	Vaginal progesterone group (n=40)	Control group (n=40)	p-value
Age (years); mean±SD	24.6±6.1	25.0±5.9	24.1±6.3	0.486
Prepregnancy BMI (kg/m^2); mean±SD	25.2±4.6	24.7±4.3	25.8±4.8	0.287
Parity; n (%)				0.502
Nulliparous	42 (52.5)	19 (47.5)	23 (57.5)	
Multiparous	38 (47.5)	21 (52.5)	17 (42.5)	
GA on admission (weeks); median (IQR)	32.1 (30.5, 33.2)	32.1 (30.3, 33.3)	32.2 (30.8, 33.1)	0.847
Symptomatic preterm labor; n (%)				1.000
Threatened preterm labor	26 (32.5)	14 (35.0)	12 (30.0)	
Preterm labor	54 (67.5)	26 (65.0)	28 (70.0)	
Route of delivery; n (%)				1.000
Vaginal delivery	55 (68.8)	28 (70.0)	27 (67.5)	
Cesarean delivery	25 (31.2)	12 (30.0)	13 (32.5)	

BMI=body mass index; GA=gestational age; IQR=interquartile range; SD=standard deviation

allocated to the control group. Notably, two participants from each group were excluded due to conditions that necessitated immediate preterm delivery. This adjustment resulted in a total of 40 participants in each group. Following the initial assessment, 26 participants were observed within the vaginal progesterone group, while 25 participants were noted within the control group during the second TVCL measurements (Figure 1).

The baseline obstetrical and clinical data, including age, pre-pregnancy body mass index (BMI), parity, gestational age on admission, symptomatic preterm labor, and route of delivery did not show significant differences between the two groups. Every participant was uniformly provided with oral acute-phase tocolysis, consisting of Nifedipine, for a continuous 48-hour period. Simultaneously, they received 6 milligrams of dexamethasone, administered in four doses within the same 48-hour timeframe (Table 1).

Indications for cesarean delivery among participants in the study included obstructive cephalopelvic disproportion, non-reassuring fetal status during labor, previous cesarean delivery in labor, and breech presentation in labor. None of the participants underwent elective cesarean delivery.

Obstetric measurements, including cervical dilatation, effacement, consistency, initial TVCL, and second TVCL also showed no significant

Table 2. Obstetric measurements data between groups

Obstetrics measurement	Total (n=80)	Vaginal progesterone group (n=40)	Control group (n=40)	p-value
Cervical dilatation (cm); median (IQR)	1 (0, 1)	1 (0, 1)	1 (0, 1)	0.749
Cervical effacement (%); median (IQR)	25 (0, 50)	25 (0, 50)	25 (0, 50)	0.606
Cervical consistency; n (%)				0.797
Soft	59 (73.8)	30 (75.0)	29 (72.5)	
Medium	20 (25.0)	9 (22.5)	11 (27.5)	
Firm	1 (1.2)	1 (2.5)	0 (0.0)	
Bishop score; median (IQR)	3 (2, 4)	3.5 (2, 4.5)	3 (2, 4)	0.635
Initial TVCL (mm); mean±SD	27.5±8.2	27.6±7.7	27.3±8.7	0.849
Second TVCL (mm); mean±SD	24.1±8.1 (n=51)	24.3±8.5 (n=26)	23.9±7.7 (n=25)	0.865

TVCL=transvaginal cervical length; IQR=interquartile range; SD=standard deviation

Table 3. Primary and secondary outcomes between groups

Outcomes	Vaginal progesterone group (n=40)	Control group (n=40)	RR (95% CI)	p-value
Latency to delivery (days); mean±SD	47.3±13.3	34.2±18.1		<0.001
GA at delivery (weeks); mean±SD	38.5±1.3	36.7±2.5		<0.001
Preterm delivery before 37 weeks; n (%)	5 (12.5)	14 (35.0)	0.35 (0.14 to 0.89)	0.036
Preterm delivery before 34 weeks; n (%)	0 (0.0)	5 (16.1)	0.09 (0.01 to 1.59)	0.053
Birth weight (g); mean±SD	2,932.6±309.9	2,627.1±517.3		0.002
Low birth weight (less than 2,500 g) ; n (%)	4 (10.0)	11 (27.5)	0.36 (0.12 to 1.04)	0.086
Apgar score at 1 minute <7; n (%)	2 (5.0)	4 (10.0)	0.5 (0.09 to 2.57)	0.675
Apgar score at 5 minutes <7; n (%)	0 (0.0)	0 (0.0)	1.0 (0.02 to 49.20)	1.000
NICU admission; n (%)	4 (10.0)	11 (27.5)	0.36 (0.12 to 1.04)	0.086
Mean differences in cervical length between the first and second TVCL measurement (mm); mean±SD	−3.2±2.8 (n=26)	−4.7±5 (n=25)		0.192

NICU=neonatal intensive care unit; TVCL=transvaginal cervical length; GA=gestational age; CI=confidence interval; RR=relative risk; SD=standard deviation

differences between the two groups (Table 2). Among the participants, 48.75% had a cervical dilation of 1 cm, 32.5% showed no cervical dilation, and the remaining participants had a cervical dilation equal to or greater than 2 cm.

For the primary outcome, the latency to delivery was significantly longer in days in the vaginal progesterone group at 47.3±13.3 versus 34.2±18.1 days (p<0.001). In terms of secondary outcomes, vaginal progesterone significantly increased gestational age at delivery from 36.7±2.5 to 38.5±1.3 weeks (p<0.001), reduced the rate of preterm delivery to 12.5% compared to 35% in the control group (p=0.036), and improved the birth weight from 2,627.1±517.3 to 2,932.6±309.9 grams (p=0.002). However, there were no significant differences between the groups in terms of mean differences of TVCL between the first and second TVCL measurements, and other adverse neonatal outcomes studied, including birth asphyxia (Apgar score lower than 7 at 1 and 5 minutes), low birth weight, and NICU admission (Table 3).

Participants reported no adverse events related to vaginal progesterone and demonstrated good compliance during the study. In the vaginal progesterone group, participants reported no difficulties applying vaginal progesterone and expressed satisfaction with the treatment.

The vaginal progesterone group had a lower risk of preterm delivery before 37 weeks compared to the control group (RR 0.35, 95% CI 0.14 to 0.89), and the number needed to treat (NNT) was 4.4 (Table 3).

Discussion

Arrested preterm labor patients usually face recurrent episodes of preterm labor and this results in preterm births. Unfortunately, there is currently no specific treatment indicated to maintain tocolysis. Researchers are attempting to demonstrate the benefits of vaginal progesterone, given its physiological role in maintaining uterine quiescence and its potential for use in maintenance tocolysis, with the aim of reducing the incidence of preterm birth. However, due to insufficient research supporting the benefits

of vaginal progesterone as maintenance tocolysis, its use and proper dosage remain controversial.

The present study demonstrated that 400 milligrams of vaginal micronized progesterone effectively prolonged the latency to delivery in cases of arrested preterm labor, with a mean extension of 13 days ($p<0.001$). This finding is consistent with a previous study by Borna and Sahabi in 2008[11], despite the present study involving a different population. These consistent results suggest the effectiveness of vaginal progesterone, regardless of ethnicity or the type of acute phase tocolysis used in the study. Furthermore, the present findings align with Hyett et al. in 2020[12], who found that 400 milligrams of vaginal progesterone, when used as maintenance tocolysis in arrested preterm labor patients with cervical length less than 25 mm, effectively increased latency preceding delivery. This is similar to this study, despite differences in cervical length among participants in the present study. This consistency with Hyett et al.'s results indicates that 400 milligrams of vaginal progesterone effectively prolong latency to delivery regardless of a patient's cervical length.

In Srisutham et al.'s study in 2020, the application of 200 milligrams of vaginal progesterone showed an insignificant reduction in preterm labor before 37 weeks. This difference from the present study may be due to the lower dosage administered in their study. The present study results suggest a more effective outcome with a higher dosage of vaginal progesterone[17].

The initiation timing of vaginal progesterone for maintenance tocolysis still varies, and no conclusive agreement has been reached. In a comparative analysis with Sirisangwon et al.'s study in 2021[13], conducted on a similar population, they initiated vaginal progesterone concurrently with the initiation of acute-phase tocolysis, whereas the present study initiated vaginal progesterone once preterm labor was arrested. Despite these variations, both studies yielded similar outcomes, demonstrating that vaginal progesterone effectively prolongs latency to delivery and significantly reduces the preterm birth rate. Therefore, it is not necessary to initiate vaginal progesterone immediately with acute-phase tocolysis. Instead, it could be started after the arrest of preterm labor to reduce exposure time to the medication and minimize its usage.

Moreover, the vaginal progesterone group had a 65% lower risk of preterm delivery before 37 weeks compared to the control group (RR 0.35, 95% CI 0.14 to 0.89, $p=0.036$), suggesting that vaginal progesterone is an effective protective factor against preterm delivery. The administration of vaginal progesterone could prevent one case of preterm delivery for every five treated patients in comparison to their untreated counterparts as calculated NNT is 4.4.

The present study demonstrated the potential benefits of 400 milligrams of vaginal progesterone as maintenance tocolysis. The results showed its ability to reduce the preterm birth rate, enhance birth weight, and extend the latency to delivery. Moreover, in conjunction with previous studies, the results provide insights into the optimal timing of initiation and route of administration, which can be useful in clinical practice. Additionally, the present study could be used for counseling patients with arrested preterm labor to discuss the choice of treatment and the benefits of vaginal progesterone as maintenance tocolysis, with the hope of reducing stress in this patient group.

The strengths of the present study include its design as a randomized controlled trial. The investigators were blinded to the patient's treatment, ensuring objectivity in the assessment. Furthermore, the outcomes measured were objective, which enhanced their reliability, accuracy, and consistency. Additionally, the present study is the first trial to exclusively use Nifedipine as acute-phase tocolysis, aiming to minimize confounding factors while ensuring efficacy in combination with vaginal progesterone. It is also one of the few studies that explore participants' satisfaction with medical application. Moreover, the progesterone dosage and formulation used in the study are easy to administer and free from undesirable side effects, making them a convenient option for home use. The adverse events related to vaginal progesterone reported in previous literature included vaginal discharge, vaginal itching, dizziness, and nausea/vomiting. However, none of the participants in the present study experienced these events[13].

Limitations inherent in the present study are the absence of a placebo and the timing of delivery in participants with a previous cesarean delivery in labor might affect the result of latency to delivery outcome. Another challenge arises from the limited capacity to assess the mean differences in cervical length between the first and second TVCL measurement due to a loss of follow-up among certain participants. As a result, the authors recommend that future investigations focus on recruiting a larger cohort to evaluate this specific outcome more comprehensively.

Conclusion

Administering 400 milligrams of vaginal progesterone, as a maintenance tocolysis, effectively prolongs latency to delivery, reduces the rate of preterm birth and improves birth weight. However, it fails to delay the shortening of the cervix and does not decrease the rate of NICU admission or occurrence of birth asphyxia.

What is already known on this topic?

Toward the end of pregnancy, the withdrawal of progesterone is considered a parturition-triggering event. Vaginal progesterone has demonstrated benefits in preventing preterm labor in patients with a history of spontaneous preterm birth.

What does this study add?

Efficacy of 400 milligrams of vaginal progesterone uses as maintenance tocolysis in arrested preterm labor.

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Conflicts of interest

The authors declare no conflict of interest.

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