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THE RELATIONSHIP BETWEEN USING NIFEDIPINE AND POSTPARTUM HEMORRHAGE IN PATIENTS WITH PRETERM LABOR

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ABSTRACT

Objective: To evaluate the risk of postpartum hemorrhage in patients treated with Nifedipine for the treatment of preterm labor. **Methods:** A prospective cohort study was conducted with 68 pregnant women admitted for preterm labor. One group of women was given Nifedipine to give time for the administration of corticosteroids for fetal lung maturity and/or control of preterm labor and another group was not given Nifedipine as they were admitted in advanced stage of labor (ie, more than or equal to 4 cm cervical dilatation). Independent/paired sample t-test, Mann-Whitney U test and Fisher's exact test were used to determine the difference of mean, median, and frequency between and within groups, respectively. MINITAB 22. Was used for data analysis. **Results:** There was more blood loss during delivery, which was statistically significant, among those who received Nifedipine compared to those who have not taken the medicine (350 mL versus 265 mL, p = 0.002). Furthermore, the decreases in hemoglobin and hematocrit were also lower among those who did not receive Nifedipine compared to those who received Nifedipine for tocolysis (1.5 g/dL versus 1.2 g/dL, p = 0.014 and 0.045 versus 0.03, p = 0.002), again, statistically significant. The need for additional uterine tonics was higher in those who received Nifedipine treatment compared to those who did not, with a statistically significant difference (26 women who used Nifedipine versus 12 women who did not use it, p-value=0.006). **Conclusion:** Nifedipine used as tocolytic showed increase hemorrhage during delivery, which was statistically significant. Greater amount of blood loss may be anticipated among those with Nifedipine intake thus helping the obstetrician in preparing for active management of postpartum hemorrhage and preventing maternal complication.

KEYWORDS: Nifedipine, preterm birth, postpartum Hemorrhage.

1. INTRODUCTION

Preterm birth (PTB)

Preterm birth (PTB) is defined as the birth of a live or stillborn baby after the 20th week and before the 37th week of pregnancy. Approximately 10% of all births occur preterm, with 85% occurring between the 32nd and 36th weeks plus 6 days of pregnancy.[1] The patient usually presents to the hospital with regular, painful uterine contractions with cervical changes (dilation and/or effacement), vaginal bleeding, and/or rupture of membranes. The diagnosis is made according to the following criteria[2]:

- Regular uterine contractions (more than or equal to 6 contractions within 60 minutes).
- Cervical dilation more than or equal to 3 cm with, effacement of 50% or more.
- Cervical length less than 2 cm on vaginal ultrasound.
- Cervical length between 2-3 cm with a positive fetal fibronectin test in the cervical fluid.

There are four main hypothesized mechanisms that lead to spontaneous preterm labor (SPTB).

1. Stress: Stress leads to early activation of the hypothalamic-medullary-adrenal (HMA) axis in the fetus.[3,4]
2. Infection and alteration of the reproductive tract microbiota, where toxins secreted by bacteria disrupt membranes and/or stimulate the production of inflammatory mediators.[5,6]
3. Decidual bleeding and placental abruption lead to increased tissue factor secretion from decidual cells, which in turn leads to thrombin production. Thrombin binds to PAR-1 receptors in the uterus, stimulating uterine contractions and weakening the structure of the fetal membranes.[7,8]
4. Uterine hyperextension (multiple pregnancy - polyhydramnios), which in turn leads to the formation of communication gaps and the formation of oxytocin receptors and inflammatory cytokines, prostaglandins, and myosin kinase, all of which synergize to trigger uterine contractions and ripen the cervix. Uterine dilation also increases the expression of genes that play an important role in collagen degradation and inflammatory

processes.[9,10]

MANAGEMENT

1- In pregnancies greater than or equal to 34 weeks with no cervical dilation and/or effacement, the patient is monitored for 4-6 hours in the hospital, and laboratory evaluations are performed for CRP and WBC. The patient can go back home after ensuring the fetus is safe and excluding abruption, amniotic inflammation, and PROM through laboratory and clinical examinations.
2- In pregnancies less than 34 weeks with cervical dilation greater than or equal to 3 cm. The patient should stay at the hospital with tocolytic medications administered for 48 hours, along with prophylactic antibiotics if necessary. Glucocorticoids are administered to mature the fetal lungs. During hospitalization, laboratory tests should repeated every 48 hours for WBC and CRP values, with careful fetal monitoring.[11,12]
3- In pregnancies less than 34 weeks with a dilatation less than 3 cm, the patient should stay at the hospital with monitoring of WBC and CRP values and fetal monitoring. Tocolytics are administered and prophylactic antibiotics are administered for 48 hours. Betamethasone is given to mature the fetal lungs, and magnesium sulfate is given to prevent potential neurological damage in pregnancies less than 32 weeks.[13,14]

Nifedipine

Nifedipine is a calcium channel blocker belonging to the dihydropyridine subclass. It is primarily used as an antihypertensive and antianginal drug.

We use the Nifedipine According to the FDA

1- Chronic stable angina, vasospasm angina, hypertension.[15-20]

Other Uses: Raynaud's phenomenon, severe hypertension during pregnancy and postpartum hypertension, High-altitude pulmonary edema, pulmonary hypertension, esophageal achalasia, distal ureteric stones, uterine relaxant (tocolytic).[21-24]

Calcium ion influx occurs through special channels during the depolarization phase of smooth muscle cells. Nifedipine inhibits the entry of calcium ions by inhibiting these channels in smooth muscle and cardiac muscle cells. Decreased calcium within smooth muscle cells leads to reduced peripheral vascular resistance and dilation of the arteries.

Nifedipine is available in both immediate-release and extended-release formulations. The immediate-release formulation begins to work within 20 minutes with a plasma half-life of approximately 4 to 7 hours, while the extended-release formulation has a duration of action of approximately 24 hours.

In preterm labor, 20 mg is administered every four hours with a half-life of approximately 7 hours.[25]

Adverse effects occur in approximately 20 to 30% of patients prescribed Nifedipine, primarily due to its vasodilatory properties.

The most common side effects include flushing, peripheral edema, dizziness, and headache. Extended-release formulations are better tolerated than immediate-release Nifedipine. Hypersensitivity reactions, such as itching, urticaria, and bronchospasm, are relatively rare. Abrupt discontinuation of the drug after prolonged use may result in rebound hypertension or angina. In general, no monitoring is required for patients taking Nifedipine. Patients should be monitored for adverse side effects such as peripheral edema, dizziness, and flushing.

Postpartum hemorrhage (PPH)

Postpartum hemorrhage (PPH) is an obstetric emergency. It is one of the top five causes of maternal death in both developing and developed countries, although the risk of death from PPH is much lower in developed countries.

Early diagnosis, prescense of necessary drugs, and the good response are critical to preventing maternal death and severe morbidity. Advance planning and preparation by caregivers are essential to ensure an appropriate response, in addition to traditional methods of hemorrhage control.[26]

The term primary or early PPH refers to postpartum hemorrhage that occurs within the first 24 hours after delivery. The Secondary or late postpartum hemorrhage (PPH) mean that the postpartum hemorrhage which occure from 24 hours to 12 weeks postpartum. A lot of methods using for diagnosing PPH are used worldwide. The classic definition of PPH (i.e., estimated blood loss of ≥500 ml after vaginal delivery or ≥1,000 ml after cesarean delivery). This consider a big problem because bleeding may not be externally visible, collection devices may mix with amniotic fluid with blood, and postpartum morbidity is rare among patients with blood losses of 500–999 ml.[27]

The American College of Obstetricians and Gynecologists (ACOG) revised its definition of PPH in 2017 as follows cumulative blood loss of ≥1,000 ml, or Bleeding associated with signs/symptoms of hypovolemia within 24 hours of delivery.[28]

Many reports are based on subjective estimates of blood loss; when blood loss is measured quantitatively, prospective studies have reported that PPH ≥ 500 ml in up to 10 percent of births. The diversity in clinical presentations of PPH has contributed to the incidence rate, and it has been noted that PPH is more common in certain races and ethnicities.[29] Although race or ethnicity is not a biological or individual cause of PPH,[30] some believe that the higher prevalence of bleeding in one group of population than another may be

due to the quality of care or attention.

The methods for bleeding stop occurs at placental separation
1- through mechanical way, where uterine contraction compresses the uterine artery branches
2- Biochemical way, where releasing of local hemostatic factors (tissue factor[31,32] and plasminogen activator inhibitor type one, respectively[33,34]) and systemic clotting factors (such as platelets and circulating clotting factors) leads to thrombosis in the uterine artery branches that supplying the placental bed. Abnormalities in these normal physiological ways lead to severe hemorrhage, especially in the third trimester of pregnancy, because uterine artery blood flow is 500 to 700 ml/minute (compared to 60 ml/minute in non-pregnant women), representing approximately 15 percent of cardiac output.

There are many risk factors for PPH occurring like:
Retained placenta/membranes - Failure to progress during the second stage of labor - Spectrum of placenta accrete - Ruptures - Vaginal delivery assisted by forceps or vaccum - Fetal macrosomia >4 kg - Hypertensive disorders (preeclampsia, HELLP syndrome [hemolysis - elevated liver enzymes, low platelets]) - Induction of labor - Prolonged first or second stage of labor[35] – placenta abruption- Severe preeclampsia.[36]

The most common causes of postpartum hemorrhage T4
1- Tone: Uterine atony
2- Trauma: Abrasions, lacerations
3-Tissues: Tissue retained after birth, blood clots, or placenta accrete (PAS)
4- Thrombin: Coagulopathy.[37]
Management Every hospital obstetrics unit should have a postpartum hemorrhage protocol and provide ongoing training to its staff regarding its use.[38]

The protocol should provide a standardized approach to assessing and monitoring a patient with postpartum hemorrhage, treating it, and notifying a multidisciplinary team.

General Objective
To evaluate the risk of postpartum hemorrhage in patients treated with Nifedipine for the treatment of preterm labor.

Specific Objectives
Comparison of the following data between the two study groups:
1. Postpartum hemorrhage, measured in ml.
2. Changes in hematocrit and hemoglobin values before and 24 hours after delivery.
3. Need for additional uterotonics.

2. METHODS

Study Design
This study is an analytical cohort study (prospective).

Study Location
Obstetrics and Gynecology Department, Tishreen University Hospital.

Study Duration
March, 2024–March, 2025.

Study Sample
Participants were selected from a database of patients who experienced preterm labor and delivered at Tishreen University Hospital.

Women were included in the study if they consented and met the study inclusion criteria. Patients were not required to be followed up from the beginning of pregnancy.

Inclusion criteria
- Singleton pregnancy with or without Nifedipine as a uterine relaxant
- Patient age between 19 and 35 years
- No history of pregnancy-related illnesses
- ≥ 5 previous deliveries
- Patients in preterm labor and gestational age between 24 and 35 weeks

Exclusion criteria
- Placenta previa
- Placenta abruption
- Pregnant women with blood clotting problems
- Macrosomia (estimated fetal weight on ultrasound greater than 4000 g)
- Polyhydramnios (amniotic fluid index greater than 24)
- Multiple pregnancies
- Patients in preterm labor treated with a drug other than Nifedipine or in combination with another drug
- Patients who refused informed consent

Withdrawal criteria
Patients who were evaluated to have any of the exclusion criteria and who withdrew their consent were excluded in the study.

Study design
- Patients were divided into two groups: the first included patients in preterm labor treated with Nifedipine and have got PTB; and the second group consisted of patients in preterm labor not treated with Nifedipine (active labor with cervical dilation greater than 4 cm, fetal abnormalities not compatible with viability) and have got PTB. The number of patients was (76). After applying the inclusion and exclusion criteria to the participants, 68 patients met the study's requirements.
- Voluntary verbal consent was obtained from the patients prior to study inclusion according to the attached informed consent form. This was followed by completing the attached questionnaire.
- A detailed medical history was taken according to

the attached form.

- A clinical examination was performed, and a detailed abdominal ultrasound of the fetus was performed.
- Blood tests (complete blood count and formula) were performed before and 24 hours after delivery, and hemoglobin and hematocrit values were recorded, as well as the change between the pre- and post-delivery hemoglobin and hematocrit values.
- The amount of postpartum bleeding lost was estimated, such as a full belly gauze equaling 250 ml, a clot the size of a fist equaling 400 ml, and the number of sanitary pads used after delivery, including the amount of suction used in cesarean sections and the amount of a under-buttock bag used in vaginal deliveries.
- The need for additional uterine tonics was recorded according to the protocol of the Obstetrics and Gynecology Department at Tishreen University Hospital.

Description of analysis

After a woman who met the inclusion criteria was enrolled in the study, a transabdominal ultrasound was performed to determine gestational age (BPD-FL), fetal viability, and amniotic fluid volume (AFI). A complete blood count (CBC) and formula were analyzed, along with baseline hemoglobin and hematocrit values. The analysis was repeated 24 hours after delivery to calculate the new hemoglobin and hematocrit values. The amount of postpartum bleeding was calculated, and the need for additional uterotonics was determined in both study groups. The women participating in the study were divided into two groups:

1. 36 delivered women after preterm labor treated with Nifedipine.
2. 32 delivered women after preterm labor not treated with Nifedipine.

Data Analysis

- After collecting the data, it was analyzed and entered into the computer using a spreadsheet from the Microsoft Office Excel 2010 office program.
- Statistical tests were conducted for each variable when necessary. Fisher test was used to study qualitative variables, and the Independent Samples Student's t test and Mann Whitney U test was used to compare arithmetic means, medians respectively.
- Statistical analysis was conducted using Minitab Statistical Software 22.

Ethical Considerations

- Informed consent was obtained from the patients in the study, with a pledge to maintain the confidentiality of the patient's personal information.
- Benefits and Risks:
- The information and data collected from the patient are confidential and are not disclosed to anyone except the study administrator.
- The procedures performed during the study are non-invasive, and do not cause harm to the patient or the fetus.
- The study will provide close monitoring of the patient and the fetus, providing optimal management for good pregnancy outcomes.

3. RESULTS

The study sample included 68 patients divided into two groups: the first group, in which 36 women used Nifedipine, and the second group, in which 32 women did not use Nifedipine.

- The mean age of patients in the first group was 26.1 years, compared to the mean age of the second group, which was 26.3 years. The P-value (0.87) was greater than 0.05, which is statistically insignificant between the two groups. Therefore, there is no relationship between patient age and Nifedipine use in the patients. Table 1
- The median gestational age at delivery in the first group was 31 weeks, while in the second group; the median was 29 weeks, which is higher than in the first group. The P-value (0.0019) was less than 0.05, which indicates a statistically significant difference between the two groups. Therefore, there is a relationship between Nifedipine use and increased gestational age in the patients. Table 1
- The number of nulliparous in the first group was 21 patients and 14 patients in the second group. The number of multiparous in the first group was 15 patients compared to 18 patients in the second group. After conducting a test of independence between the two groups, the P-value (0.33) was greater than 0.05, indicating independence between the two groups. There was no statistically significant relationship between the women's obstetric history and the use of Nifedipine in the patients. Table 1
- The first group included 17 patients who delivered by cesarean section, compared to 15 women who delivered by cesarean section in the second group. Meanwhile, 19 women delivered by vaginal delivery in the first group, compared to 17 patients who delivered by vaginal delivery in the second group. After conducting a test of independence between the two groups, the P-value (1) was greater than 0.05, indicating independence between the two study groups and, consequently, no relationship between Nifedipine use and the method of delivery. Table 1
- The mean duration of cesarean delivery in the first group was 33.35 minutes, compared to 30.07 minutes in the second group, which is smaller than the mean in the first group. The P-value was 0.008, which is less than 0.05 and therefore statistically significant, indicating an association between Nifedipine use and an increase in the duration of cesarean delivery. Table 1
- The median duration of vaginal delivery in the first group was 10 hours, compared to 9 hours in the second group. The P-value was 0.58, which is greater than 0.05, indicating no statistically significant difference, meaning there is no

association between Nifedipine use and the duration of vaginal delivery. Table 1

- Baseline hemoglobin values before birth were greater than postpartum values in both study groups. The median change in hemoglobin values before and after birth in the first group was 1.5 g/dL, and the median change in hemoglobin in the second group was 1.2 g/dL. The P-value (0.014) was less than 0.05, indicating a statistically significant difference between the two groups. Therefore, there is a relationship between Nifedipine use and greater postpartum hemoglobin change. Table 2
- Baseline hematocrit values before birth were greater than postpartum values in both study groups. The median change in hematocrit values in the first group was 0.045, and the median change in the second group was 0.030. The P-value (0.002) was less than 0.05, indicating a statistically significant difference. Therefore, there is a relationship between Nifedipine use and greater postpartum hematocrit change. Table 2
- The average postpartum hemorrhage ranged from 200-600 ml in the first group, compared to 100-500 ml in the second group. The median amount of bleeding was 350 ml in the first group, compared to 265 ml in the second group. The P-value (0.002) was less than 0.05, indicating a statistically significant difference between the two groups. Therefore, there is a relationship between Nifedipine use and postpartum hemorrhage in women. Table 2
- 26 patients required additional uterine tonics (according to the obstetrics and gynecology department protocol used at Tishreen University Hospital for administering uterine tonics) in the first group, compared to 12 patients in the second group. Meanwhile, 10 patients in the first group and 20 patients in the second group did not require additional uterine tonics beyond the protocol. The P-value (0.006) was less than 0.05, indicating no independence between the two groups. However, there was a statistically significant relationship between the use of Nifedipine and the need for additional uterine tonics after delivery. Table 2

***Table 1: Demographic profile of 68 patients group 1 and group 2.**

	Group 1 (36)	**Group 2 (32)**	**P-value**
	Frequency(%);Mean +SD; Median(Rang)		
Age	26.1+4.5	26.3+4.4	0.87 *
Age of gestation	31 (27-35) w	29 (24-35) w	0.019 +
Parity Nulliparous Multipara	 21 (58.3%) 15 (41.7%)	 14 (43.75%) 18 (56.25%)	0.33 *f*
Manner of delivery SVD CS	 19 (%52.8) 17(47.2 %)	 17 (54%) 15(46%)	1 *f*
No. of hours of labor	10 (8-12) H	9 (8.5-14) H	0.58 +
No. of minute of SC	33.35+2.32 Min	30.07+3.15 Min	0.008 *

Statistical test used ** – Independent Sample T-test; +-Mann-Whitney U test; f – Fisher's Exact test.*

***Table 2: The change in Hgb, Hct, PPH amount, the need for additional uterotonics.**

	Group 1 (36)	**Group 2 (32)**	**P-value**
	Frequency(%), Median(Rang)		
Hemoglobin Baseline Postpartum Hgb difference	 12.3 (10-13.3) g/dl 10.5 (9-11.5) g/dl 1.5 (0.03-2.83) g/dl	 11.95 (10.5-13.2) g/dl 10.4 (9.6-12.5) g/dl 1.2 (0.2-2.2) g/dl	 0.014 +
Hematocrit Baseline Postpartum Hct difference	 0.44 (0.40-0.47) 0.39 (0.36-0.43) 0.045 (0.01-0.11)	 0.44 (0.40-0.48) 0.40 (0.35-0.42) 0.030 (0.01-0.2)	 0.002 +
Postpartum hemorrhage amount	350 (200-600) ml	265 (100-500) ml	0.002 +
Need for uterotonics Yes No	 26 (72.2 %) 10 (27.8%)	 12 (37.5%) 20 (62.5%)	0.006 *f*

Statistical test used *+-Mann-Whitney U test; f – Fisher's Exact test*

***Table 3 Nifedipine profile in group 1.**

Nifedipine profile	Frequency (%)Median (Rang)
Initial dose 40 mg	36 (100%)
Succeeding dose 10 mg 20 mg	23 (63.9%) 13 (36.1%)
Frequency of giving succeeding dose (hours)	6 (4-8) hrs.
Numbers of days	4 (2-6) day
Number of hrs. from last intake(hours)	24 (6-72) hrs.

4. DISCUSSION

As a result of our study we can say that, there was more hemorrhage during delivery among those who received Nifedipine(group 1) compared to those who did not receive the medicine(group 2), which was statistically significant (p=0.002).

Furthermore, the decrease in hemoglobin and hematocrit were also lower among those who did not receive Nifedipine (group 1) compared to those who received (group 2) Nifedipine for tocolysis (1.5 g/dL versus 1.2 g/dL, p=0.045 and 0.030, p=0.002), versus 0.05 which were statistically significant.

This is a pilot study in Syria. There are some new studies in the world talking about the effect of Nifedipine or another tocolysis on the postpartum blood loss obtained among women in preterm labor.

• A retrospective study conducted by Huseyin Kiyak and colleagues (Turkey 2023) included 486 patients who experienced preterm labor from 2012 to 2019. The sample was divided into:

- Case group (240 women): received Nifedipine treatment.
- Control group (246 women): did not receive any preterm labor suppressant treatment.
- The case group was divided into subgroups based on the last Nifedipine dose between 24 and 72 weeks.
- Hemoglobin, hematocrit, and platelet counts were measured before and six hours after delivery, and postpartum bleeding was calculated.
- No statistically significant differences were observed in hemoglobin and hematocrit values before and after delivery between the two groups. However, the difference in hemoglobin and hematocrit values before and after delivery was greater in the subgroup receiving Nifedipine doses 24 hours before delivery, but not at 72 hours or weeks.

A retrospective study conducted by Hua-Lin Lee, Kuo-Ching Lu, and colleagues (Taiwan, 2020) conducted a population-based cohort of women who experienced preterm labor and early cesarean delivery between 2002 and 2006 in Taiwan. The study sample was divided into two groups:

Case group (15,317 women): who received labor-inducing treatments.

Control group (244,096 women): who did not receive any treatment.

The study aimed to determine the risk and incidence of bleeding in patients treated with various medications. After conducting statistical analyses, the incidence was 11.7% versus 2.6%, with a p-value less than 0.001.

The results showed statistically significant differences in the incidence of bleeding between the two groups. The risk varied depending on the medication used, with retroviral therapy accounting for 80%, followed by combination therapies (8.5%), magnesium sulfate (4.6%), calcium channel blockers (3.8%), prostaglandin synthesis inhibitors (0.5%), and nitrates (0.1%).

A prospective cohort study conducted by Ma. Sheryll R. de Jesus and colleagues (Philippines, 2018) in the Philippines included 66 pregnant women who experienced preterm labor treated with Nifedipine. The study sample was divided into two groups:

Case group (24 women): received Nifedipine

Control group (42 women): did not receive the drug.

The mean amount of post-cesarean bleeding in the case group was 350 ml, a statistically significant difference compared to the control group (250 ml).

There was greater bleeding, according to standard deviations in hemoglobin and hematocrit, in the case group compared to the control group, with a statistically significant difference of 0.014 Hgb and 0.010 Hct.

A retrospective study conducted by Soo Ran Choi and colleagues (South Korea, 2017) at the Department of Obstetrics and Gynecology at Inha University Hospital, South Korea, included 296 women who experienced preterm labor treated with tocolytic drugs and delivered prematurely. Patients' hemoglobin and hematocrit levels were measured before and after delivery, and statistical analysis determined whether delivery occurred within the half-life of the tocolytic drug. Hemoglobin and hematocrit levels decreased significantly after delivery in patients who delivered within the half-life of the drug, and their blood transfusion rates increased.

5. CONCLUSION

Our research showed that Nifedipine used as a Tocolytic (group 1) increased blood loss during delivery among those women in preterm labor compared to those who did not take Nifedipine(group 2) the difference was statistically significant.

This is reflected in the greater decrease in hemoglobin and hematocrit from baseline compared to 24 hours post-delivery among those who took Nifedipine.

We found some recommendations after we do this research:

- We studied nifedepine because it the most common tocolytic in Syria, but there are many other tocolytic agents.more researches must do about the relationship between different tocolytic agents and postpartum hemorrhage.
- More researches have to do for comparative between different types of tocolytics and postpartum hemorrhage, and the most effective and least risky drug should be identified as a cause of postpartum hemorrhage.
- Some differences have been observed in patients treated with the drug in terms of the amount of bleeding, the dose used, or the last dose given before delivery. Therefore, we recommend conducting future statistical studies regarding the optimal dose for appropriate therapeutic effect and the amount of postpartum hemorrhage, and determining the optimal time to discontinue the drug before delivery, if that possible.
- Pay attention to patients who treated with the drug by monitoring the amount of bleeding that occurs after delivery. And be ready to save the patient life, such as securing a large intravenous line, transferring intravenous fluids, attention to vital signs and uterine (safety ball), and securing spare blood units before delivery.

Limitations of the study

The differences in the dosing of the interventions in each study may account for differences in their results.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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