International Journal of Gynecology and Obstetrics 104 (2009) 44–48

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Effect of oral N-acetyl cysteine on recurrent preterm labor following treatment for bacterial vaginosis

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ARTICLE INFO

Article history:
Received 2 May 2008
Received in revised form 13 August 2008
Accepted 26 August 2008

Keywords:
Bacterial vaginosis
N-acetyl cysteine
Preterm labor

ABSTRACT

Objective: To evaluate the effect of N-acetyl cysteine (NAC) on gestational age at delivery in women with previous preterm labor and bacterial vaginosis. *Methods:* A randomized, double-blind, placebo-controlled trial with 280 women between 16 and 18 weeks of pregnancy who had 1 previous preterm birth and had just been successfully treated for bacterial vaginosis with metronidazole for 1 week. The women were randomized to receive 0.6 g of NAC per day plus 17-hydroxyprogesterone caproate (17-OHPC) or placebo plus 17-OHPC until 36 completed weeks of pregnancy or active labor. A vaginal swab was taken during labor. *Results:* Reaching 36 weeks of pregnancy was more frequent ($P<0.05$) and gestational age at delivery was significantly higher in the NAC than in the placebo group (37.4 weeks ± 0.4 weeks vs 34.1 weeks ± 1.2 weeks, $P<0.05$). The discontinuation rate was 11.4% in the NAC group. *Conclusions:* Oral NAC was found to reduce the recurrence of preterm birth in patients with bacterial vaginosis.

1. Introduction

Premature birth is the most prevalent cause of perinatal mortality and long-term morbidity in low-income countries [1]. Fetal infection, inflammation, and previous preterm delivery are pivotal risk factors for preterm birth and neonatal brain injury [2].

Ascending infection with bacterial vaginosis during pregnancy is associated with, and a risk factor for, preterm delivery and low birth weight [3–5]. A recent Cochrane Review suggests that infection screening and treatment programs for pregnant women may reduce preterm birth rates and low preterm birth weight [6]. Most studies have shown metronidazole and clindamycin to be the drugs of choice for treating bacterial vaginosis [7]. Antimicrobial treatment is, however, not sufficient for the prevention of preterm birth [8] and the problem is complicated by inflammatory and anti-inflammatory responses [9].

N-acetyl cysteine (NAC)—the acetylated precursor of both amino acid L-cysteine and reduced glutathione—is a safe, well-tolerated mucolytic drug that softens tenacious mucous secretions [10] and enhances glutathione S-transferase activity [11]. Oral NAC has a low bioavailability, between 4% and 10%, due to deacetylation during first-pass metabolism in the small intestine and liver. It reaches its peak plasma level after 1 hour and disappears from the plasma after 12 hours. NAC stimulates glutathione synthesis, promotes detoxification, and acts directly as a scavenger of free radicals [12]. Consequently, it is a powerful antioxidant and a potential treatment option for diseases characterized by the generation of free oxygen radicals [13].

The aim of the present study was to evaluate the effect of NAC (in conjunction with metronidazole and 17-hydroxyprogesterone caproate [17-OHPC]) on gestational age at delivery in women with a history of preterm labor and bacterial vaginosis.

2. Materials and methods

2.1. Recruitment and inclusion criteria

The study was conducted at The Women's Health Center, Assiut University, Egypt, from January through December 2007. Patients were eligible for inclusion if they were between the 16th and 18th weeks of pregnancy, tested positive for bacterial vaginosis, and had a history of 1 spontaneous preterm labor of a live-born singleton between 20 weeks and 36 weeks plus 6 days of gestation. The study was approved by the review board of the Department of Obstetrics and Gynecology of Assiut University. Written informed consent was provided by the participants.

Exclusion criteria were age older than 35 years or younger than 20 years; threatened abortion in the current pregnancy; uterine contractions at the time of recruitment; unwillingness to participate; irregular and/or uncertain menstrual dates; rupture of membranes; documented history or clinical examination suggestive of an incompetent cervical os; previous cesarean delivery; cerclage performed in the previous or current pregnancy; or possible risks for preterm birth in the current or previous pregnancy such as twin pregnancy, intrauterine fetal

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0020-7292/$ – see front matter
doi:10.1016/j.ijgo.2008.08.026

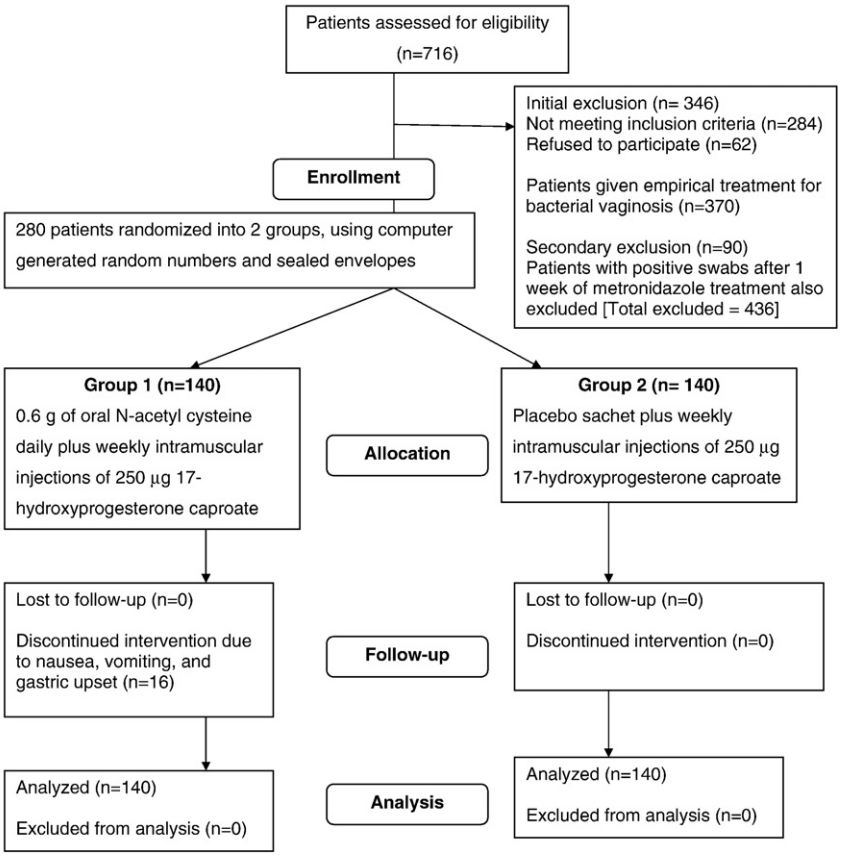

Fig. 1. Patient recruitment, randomization, follow-up, and analysis.

death, malpresentation, known fetal anomaly, progesterone or heparin treatment during the current pregnancy, hypertension, and/or seizure disorders.

Gestational age was determined on the basis of the last menstrual period, confirmed by an ultrasound scan conducted between 6 and 14 weeks of gestation and calculated in menstrual weeks.

The clinical work-up included a history taken prior to enrollment, examination, obstetric ultrasound evaluation, and biophysical profile taken after 32 weeks of pregnancy per department protocol. The patients who accepted to participate and met the inclusion criteria were treated for bacterial vaginosis prior to enrollment with 250 mg oral metronidazole 3 times per day for 1 week, and then tested for bacterial vaginosis 1 week after treatment with a vaginal swab. Criteria used to diagnose bacterial vaginosis were those of Amsel et al. [14]. The patients who tested negative for bacterial vaginosis after treatment were included in the study, and those who tested positive were excluded.

2.2. Randomization and follow-up

The patients were randomly allocated to 2 treatment groups using computer-generated numbers in sealed envelopes. Treatment was started immediately after the test result was known, and continued until 36 completed weeks of pregnancy or active onset of labor. The patients were randomized to receive either a daily dose of 0.6 g of NAC in oral effervescent form (Acetylcysteine; Sedico, Egypt, sachet form) plus weekly intramuscular injections of 250 μg of 17-OHPC (Cidolut depot; Sedico); or a daily placebo sachet plus the same progesterone injection as in the NAC group. The placebo sachets were specially manufactured to look identical to the NAC sachets. The sachets were placed in sacs and then stored in envelopes numbered from 1 to 280. The envelopes were numbered and randomized according to computer-generated randomization tables to ensure an equal number of patients in each arm. Throughout the trial, access to the randomization code was available only to the pharmacist who manufactured the placebo and packed the envelopes and was not available to any of the treating physicians or patients.

The patients were followed up for the occurrence of uterine contractions at routine prenatal clinic visits every 2 weeks. If contractions occurred between the prenatal visits the patients

Table 1
Demographic characteristics and clinical outcomes of the study participants [a]

Characteristic	NAC group (n = 140)	Placebo group (n = 140)	*P* value
Age, y	26.5 ± 2.4	25.9 ± 2.9	NS
Parity	2.4 ± 0.6	2.2 ± 0.2	NS
Gestational age at time of randomization, wk	17.4 ± 0.9	17.6 ± 1.1	NS
Patients developing contractions	14 (10.0)	38 (27.1)	<0.05
Patients receiving tocolysis	4 (2.9)	12 (8.6)	NS
Patients reporting side effects	26 (18.6)	14 (10.0)	NS
IUGR	4 (2.9)	12 (8.6)	NS
Patients completing 36 weeks of pregnancy	132 (94.3)	78 (55.7)	<0.05
Gestational age at delivery, wk	37.4 ± 0.4	34.1 ± 1.2	<0.05
Patients with spontaneous labor	83 (59.3)	128 (91.4)	<0.05
No. of patients with induced labor	57 (40.7)	12 (8.6)	<0.001
Fetal weight, g	3107.3 ± 232.4	2715.2 ± 357.2	<0.01
NICU admissions	12 (8.6)	54 (38.6)	<0.001
NICU admissions>24 h	2 (1.4)	24 (17.1)	<0.0001
Neonatal deaths	4 (2.8)	20 (14.3)	<0.01
Neonates discharged home	134 (95.7)	80 (57.1)	<0.05

Abbreviation: NAC, N-acetyl cysteine; NS, not significant; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.
[a]Values are presented as mean ± SD or number (percentage).

Table 2
Breakdown of discontinuation rate and side effects in the N-acetyl cysteine group

Variable	No. (%)
Discontinued treatment	16 (11.4)
Nausea	1 (0.7)
Vomiting	13 (9.3)
Gastric upset	2 (1.4)
Continued with no complaints	86 (61.4)
Continued and tolerated complaints	38 (27.1)
Nausea	9 (6.4)
Vomiting	3 (2.1)
Gastric upset	26 (18.6)

reported to the emergency department of the hospital. Per department protocol, a weekly biophysical profile was taken after 32 weeks of pregnancy and when complications occurred, and tocolysis was initiated when uterine contractions before 36 completed weeks, although insufficient to establish active labor, were associated with cervical changes. Active labor was defined as at least 3 uterine contractions, 40 seconds each, reaching 50 mm on an external tocodynamometer, and/or progressive cervical dilation reaching at least 5 cm, and/or rupture of membranes. A vaginal examination was conducted under strict sterile conditions. Once the patient was in labor a vaginal swab was taken and checked for bacterial vaginosis. After delivery, all patients were admitted to the postpartum ward for 1 week. Neonates who did not need admission to the neonatal intensive care unit (NICU) or who were discharged from the unit within the week were sent home with their mothers.

2.3. Sample size and statistical analysis

Sample size was based on the work of Hauth et al. [15], who found a 49% rate of preterm birth among women at high risk for preterm birth who also had bacterial vaginosis. A 30% reduction in incidence was considered acceptable. The sample size was calculated for a 5% chance of a type I error and 80% power. Forty-nine patients were needed in each arm. The analysis was performed according to the intention-to-treat principle. The primary outcome was the proportion of patients completing 36 weeks of pregnancy. Secondary outcomes included mean gestational age at the time of labor onset and the number of neonates discharged home. Data were analyzed using SPSS software, version 13.0 (SPSS, Chicago, IL, USA). The independent-sample *t* test was used for assessing the significance of the difference between continuous variables. The χ^2 test or the Fisher exact test was used to assess the statistical significance of categorical variables. $P<0.05$ was considered statistically significant.

3. Results

This was a randomized, double-blind, placebo-controlled trial. Of 716 patients assessed for eligibility, 62 refused to participate and 284 did not meet the inclusion criteria. The remaining 370 patients were treated with metronidazole for bacterial vaginosis and the 90 who tested positive 1 week after treatment were also excluded. The remaining 280 patients were randomized to 2 treatment groups of 140 patients. Fig. 1 shows the flow of participants through the study.

The NAC plus progesterone group and the placebo plus progesterone group were similar in age ($P=0.74$), parity ($P=0.09$), gestational age at the time of randomization ($P=0.18$), number of patients who received tocolysis ($P=0.052$), and number of patients reporting adverse effects of the treatment ($P=0.08$) (Table 1). The number of patients with uterine contractions before 36 weeks was significantly higher in the placebo group ($P<0.05$). Although the number of cases of intrauterine growth restriction (IUGR) was higher in the placebo group, the difference was not significant ($P=0.052$) (Table 1).

Significantly more patients completed 36 weeks of gestation in the NAC group than in the placebo group (132 vs 78, $P<0.05$) (Table 1). The relative risk (RR) for being delivered after 36 weeks was 0.80 in the NAC group (95% confidence interval [CI], 0.69–0.93). In the NAC group fewer patients had spontaneous labor (83 vs 128, $P<0.05$) and more patients had induced labor (57 vs 12, $P<0.001$). In the NAC group the mean gestational age at birth was also significantly greater (37.4±0.4 weeks vs 34.1±1.2 weeks, $P<0.05$), as was the birth weight (3107.3±232.4 g vs 2715.2±357.2 g, $P<0.01$), and there were fewer admissions to the NICU ($P<0.001$), fewer admissions to the unit necessitating more than 24 hours of care ($P<0.0001$), and more neonates discharged early ($P<0.05$) (Table 1).

Sixteen patients (11.4%) discontinued taking NAC owing to nausea, vomiting, and/or gastric upset (Table 2). The discontinuation took place after 10 to 14 days. The patients who discontinued the treatment had baseline characteristics similar to those who completed the treatment.

Table 3 provides a life table analysis of pregnancy continuation in both groups. There were more continuing pregnancies in the NAC group at 28 weeks (140 vs 126, $P=0.54$), 32 weeks (137 vs 109, $P=0.19$), 34 weeks (135 vs 93, $P<0.05$), and 36 weeks (132 vs 78, $P<0.05$).

Table 3
Life table analysis for the maintenance of pregnancy

	NAC group (n=140)				Placebo group (n=140)			
Weeks of gestation	Number continuing pregnancy	Numbers delivered	Cumulative continuation rate	Standard error	Number continuing pregnancy	Numbers delivered	Cumulative continuation rate	Standard error
20	140	0.00	1.00	0.00	140	0	1.00	0.00
24	140	0.00	1.00	0.00	140	0	1.00	0.00
25	140	0.00	1.00	0.00	138	2	0.96	2.00
26	140	0.00	1.00	0.00	135	5	0.95	2.00
28	140	0.00	1.00	0.00	126	14	0.86	3.00
30	139	1	0.99	1.00	115	25	0.81	3.00
31	138	2	0.98	1.00	113	27	0.78	4.00
32	137	3	0.96	2.00	109	31	0.67	4.00
33	135	5	0.96	2.00	94	46	0.66	4.00
34	135	5	0.94	2.00	93	47	0.56	4.00
35	132	8	0.94	2.00	79	61	0.56	4.00
36	132	8	0.78	4.00	78	62	0.31	4.00
37	109	31	0.51	4.00	44	96	0.16	3.00
38	71	69	0.24	4.00	22	118	0.08	2.00
39	33	107	0.09	2.00	11	129	0.02	1.00
40	13	127	0.01	1.00	3	137	0.01	1.00
41	1	139	0.00	0.00	1	139	0.00	0.00

Abbreviation: NAC, N-acetyl cysteine.

Table 4
Clinical outcomes in patients with bacterial vaginosis at onset of labor [a]

Outcome	NAC group (n=140)	Placebo group (n=140)	*P* value
No. of patients with BV	64 (45.7)	82 (58.6)	NS
Patients completing 36 weeks of pregnancy	58/64 (84.0)	32/82 (39.0)	<0.01
Gestational age at delivery, wks	38.4±1.2	33.1±1.3	<0.01
Patients with spontaneous labor	28/64 (43.8)	72/82 (87.8)	<0.05
Patients with induced labor	36/64 (56.2)	10/82 (12.2)	<0.001
Fetal weight, g	2902.5±257.2	2699.3±182.9	<0.01
Neonatal admission to ICU	8/64 (12.5)	36/82 (43.9)	<0.01
Neonatal deaths	4/64 (6.3)	14/82 (17.1)	NS
Neonates discharged home	60/64 (93.7)	42/82 (51.2)	<0.05

Abbreviations: NAC, N-acetyl cysteine; BV, bacterial vaginosis; ICU, intensive care unit; NS, not significant.
[a]Values are given as mean±SD or number (percentage).

We compared the subgroups of women in the NAC and placebo groups who tested positive for bacterial vaginosis at onset of labor (64 vs 82, $P=0.38$) and those who tested negative (76 vs 58, $P=0.41$). Compared with the placebo subgroup with positive results for bacterial vaginosis at onset of labor, in the corresponding NAC subgroup more patients completed 36 weeks of pregnancy (58 vs 32), $P<0.01$; RR for delivering after 36 weeks, 0.73 [95% CI, 0.59–0.89]); the gestational age at delivery was higher (38.4±1.2 weeks vs 33.1±1.3 weeks, $P<0.01$); the birth weight was higher (2902.5±257.3 g vs 2699.3±182.9 g, $P<0.01$); more neonates were discharged home (60 vs 42, $P=0.02$; RR, 0.77 [95% CI, 0.63–0.96]); and there were fewer admissions to the NICU ($P<0.01$) and fewer neonatal deaths ($P=0.08$). Fewer patients in this NAC subgroup had spontaneous labor ($P<0.05$) and there were more labor inductions in this subgroup than in the corresponding placebo subgroup (Table 4).

Compared with the placebo subgroup with negative results for bacterial vaginosis at onset of labor, in the corresponding NAC subgroup more patients completed 36 weeks of pregnancy, although this was not significant ($P=0.42$; RR for delivering after 36 weeks, 0.91 [95% CI, 0.72–1.15]); the gestational age at delivery was higher ($P=0.12$); the birth weight was higher ($P<0.01$); more neonates were discharged home with their mothers after a week [$P=0.13$, OR 0.67; RR 0.84, (95% CI, 0.93–1.67] and there were fewer admissions to the NICU ($P<0.001$) and fewer neonatal deaths ($P<0.01$). Although the difference was not significant ($P=0.26$), fewer patients had spontaneous labor in this NAC subgroup than in the corresponding placebo subgroup; however, there were more labor inductions in this subgroup ($P<0.01$) (Table 5).

Ten patients in the NAC group and 9 in the placebo group were delivered by cesarean. The indications for cesarean delivery were arrested descent of the head (n=2), arrested cervical dilation (n=4), IUGR with nonreassuring antepartum fetal tests (n=5), ominous intrapartum fetal heart rate pattern (n=3), and chorioamnionitis with failed induction (n=5).

Table 5
Clinical outcomes in patients without bacterial vaginosis at onset of labor

Outcome	NAC group (n=140)	Placebo group (n=140)	*P* value
No. of patients without BV	76 (54.3)	58 (41.4)	NS
Patients completing 36 weeks of pregnancy	74/76 (97.4)	46/58 (79.3)	NS
Gestational age at delivery, wks	36.5±1.6	35.4±1.8	NS
Patients with spontaneous labor	55 (72.4)	56 (96.6)	NS
Patients with induced labor	21 (27.6)	2 (3.4)	<0.01
Fetal weight, g	3196.6±394.8	2921.7±404.1	<0.01
NICU admissions	4/76 (5.3)	18/58 (31.0)	<0.001
Neonatal deaths	0/76 (0.0)	6/58 (10.3)	<0.01
Neonates discharged home	74/76 (97.4)	38/58 (65.5)	NS

Abbreviations: NAC, N-acetyl cysteine; BV, bacterial vaginosis; NICU, neonatal intensive care unit; NS, not significant.
[a]Values are given as mean±SD or number (percentage).

4. Discussion

We evaluated the effect of adding NAC to the treatment of women with previous preterm birth and bacterial vaginosis. The outcomes were more favorable for women in the NAC group than for those in the placebo group regardless of bacterial vaginosis status at the onset of labor.

The use of NAC during pregnancy has been described in the literature. It is used to treat acetaminophen poisoning throughout pregnancy [16] and to prolong pregnancy in patients with pre-eclampsia and HELLP (hemolytic anemia, elevated liver enzymes, and low platelet count) syndrome [17], and studies have investigated its anti-inflammatory and antioxidant effects as well as its ability to cross the placenta and increase fetal liver glutathione levels [18]. NAC has an anti-inflammatory effect that interferes with term and preterm labor in humans [19,20] and with the inflammatory cascade during pregnancy in rats [21]. We hypothesized that these effects would add to the effect of progesterone treatment in our high-risk group.

In the present study, the patients treated with NAC who tested positive for bacterial vaginosis at labor onset were significantly more likely to have completed 36 weeks of pregnancy and have neonates of greater gestational age at delivery than those in the corresponding placebo subgroup. However, NAC did not significantly prolong pregnancy in patients with pre-eclampsia and HELLP syndrome (mean duration, 29±4 weeks vs 28±2 weeks), as it had to be terminated owing to a deterioration of the maternal condition [17]. Buhimischi et al. [18] found a protective effect of NAC against preterm labor and fetal death associated with infection in mice on day 16 of gestation. This is explained by the protective effect of NAC against inflammatory response and fetal long-term sequelae described by Beloosesky et al. [21]. NAC inhibits the inflammatory response irrespective of whether infection started before or after treatment initiation with the drug [21]. We propose that the anti-inflammatory, choriodecidual-protecting effect of NAC prevents preterm birth in the presence of bacterial vaginosis.

Oxidative stress, which is associated with pregnancy and infection, activates nuclear factor kappa B (NF-κB), a major transcription factor for tumor necrosis factor alpha, and interleukins 6 and 8. This leads to increased prostaglandin and cyclo-oxygenase-2 synthesis [22] and induces the expression of matrix metalloproteinase P, which is implicated in preterm labor [19]. Specific inhibitors for activating NF-κB could be clinically useful in the treatment of preterm labor associated with infection [1,23]. The incubation of amnion and choriodecidua with NAC was shown to inhibit lipopolysaccharide-stimulated activation of matrix metalloproteinase 9, with an associated decrease in 8-isoprostane [23]. NAC inhibits NF-κB activation, the subsequent phospholipid metabolism, proinflammatory cytokine release, and protease activity in human fetal membranes and the myometrium [23]. These mechanisms possibly led to the clinical trend observed for higher gestational age at delivery and the higher number of patients completing 36 weeks of pregnancy in the NAC subgroup testing negative for bacterial vaginosis at labor onset compared with the corresponding placebo subgroup. The mechanisms may have interfered with the inflammatory cascade associated with term and preterm labor [19,20], and they may also have led to the higher incidence of labor induction and lower incidence of spontaneous labor in the NAC group, irrespective of the presence of vaginosis. Because of the low bioavailability of the drug, higher doses and a larger sample size may show a significant protection in the subgroup testing negative for bacterial vaginosis at onset of labor.

Because no well-controlled trials of NAC have been conducted with pregnant women, it was categorized by the US Food and Drug Administration as a pregnancy category B medication. Human studies have shown NAC to have few adverse effects and a high maternal and fetal safety [16,17,24], and animal studies have shown it to be protective against both methyl mercury embryotoxicity in mice [25] and the teratogenic effect of diabetic serum in cultured rat embryos

[10]. We found no major maternal or fetal adverse effects of its use, apart from an 11.4% discontinuation rate due to nausea and vomiting.

Limitations of the present study include not measuring plasma levels of the drug or choriodecidual tissue expression of inflammatory cytokines. In light of its low bioavailability, the choice of the appropriate dose still requires further investigation. Our study could not determine the exact mechanism of action of the drug in the presence or absence of bacterial vaginosis. It remains to be evaluated whether NAC can be used when preterm labor is threatening.

We conclude that in women with previous preterm birth and bacterial vaginosis, 0.6 g of NAC can be taken orally along with progesterone after 16 weeks of pregnancy to protect against preterm birth recurrence and improve neonatal outcome. More studies are needed to confirm these findings.

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