ORIGINAL ARTICLE

A Comparison of the Umbilical Artery Doppler Indices between Pregnancies with Advanced and Normal Maternal Age in the Second Trimester

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Objective: To compare the pulsatile index (UA-PI), resistance index (UA-RI), and systolic/diastolic ratio (UA-S/D) of the umbilical artery between pregnant women with advanced maternal age (AMA) and normal maternal age.

Materials and Methods: Participants were pregnant women who attended antenatal care at the maternal-fetal medicine unit at Bhumibol Adulyadej Hospital, Royal Thai Air Force, Bangkok, Thailand. The present study was conducted between February and December 2022. Participants who met inclusion criteria were classified as study for the patients aged 35 years and older, and control groups for the patients younger than 35 years old. All participants underwent ultrasonography for umbilical artery Doppler velocimetry measurement including UA-PI, UA-RI, and UA-S/D. Demographic characters of both study and control groups were included for statistical calculation.

Results: Five hundred pregnant women with gestational age between 18 and 24 weeks were enrolled. The mean age of the study and the control group were 37.9 and 26.0 years, respectively. Participants in the study group have higher BMI than the control group. The study and the control group had comparable diastolic and systolic blood pressure. The mean (standard deviation) of UA-PI, UA-RI, and S/D ratio of the study/control group were 1.33±0.21/1.27±0.22, 0.77±0.1/0.74±0.09, and 4.24±0.98/3.95±0.97, respectively, with statistical significance. The study group had a significantly higher number of large for gestational age (LGA), pregnancy induced hypertension (PIH), and gestational diabetes mellitus (GDM) than the control group.

Conclusion: AMA pregnancy had higher UA-PI, UA-RI, UA-S/D, incidence of PIH, GDM, and LGA than those age less than 35 years.

Keywords: Advanced maternal age; Umbilical artery Doppler indices; Second trimester

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Advanced maternal age (AMA) is defined as pregnancy when maternal age at estimated delivery age (EDC) is more than 35 years old[1]. One of the common complications among AMA parturient is decreased uteroplacental perfusion. This leads to an increase in adverse maternal and fetal complications compared to those who are less than 35 years of age. Common maternal complications are pregnancy induced hypertension (PIH), fetal growth restriction (FGR), and gestational diabetes mellitus (GDM)[2,3]. Spontaneous miscarriage and stillbirth are often found in fetus of AMA parturients[4-9].

Fetal umbilical arteries carry deoxygenated blood and run from the fetus to the placenta. The umbilical cord provides a connection between the mother and her fetus. Good placental hemodynamics, represented by normal value of umbilical artery Doppler indices (UDI) and uterine artery Doppler indices. UDI is a useful indicator for placental hemodynamic and represents fetoplacental vascularization[10].

UDI study includes pulsatile index (UA-PI), resistance index (UA-RI), and systolic to diastolic radio (UA-S/D) measurement of the umbilical artery. Pulsatile index (PI) is the ratio between the pulse pressure or the difference between systolic and the diastolic blood pressure and mean arterial pressure.

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Resistance index (RI) is the ratio between the pulse pressure and the systolic blood pressure. Systolic and diastolic ratio (S/D) is the ratio between the systolic and diastolic blood pressure[1].

Measurements of UDI are usually performed with indications of complicated or high-risk pregnancies, such as FGR and multifetal pregnancy. Reduction of diastolic blood pressure increases the pulsatile index. Reduction of end diastolic blood pressure affects fetal growth, which causes FGR[1,11].

Assessment of UDI in addition to other antenatal testing provides an early detection of ominous signs, for example FGR and PIH[1]. With detection of these outcomes, obstetricians could plan for pregnancy termination at an appropriate gestational age. Previous literature reported the benefits of UDI measurement in low-risk pregnancy. UDI measurement could be used to predict catastrophic event such as intrauterine fetal death, so that an appropriate decision can be discussed with pregnant woman as early as possible[12-14].

The normal UDI values of pregnant women in the second trimester have been widely demonstrated in earlier research[15-17]. Literature also reported the association between high UA-PI and UA-RI in the second and third trimesters with poor neonatal outcomes, namely small for gestational age (SGA) and low postpartum umbilical artery pH[10,13,15-22].

The aim of the present study was to compare umbilical Doppler indices between pregnancies with advanced and normal age. Pregnancy outcomes between groups were also determined.

Materials and Methods

The present study was a prospective analytical study that investigated pregnant women age between 18 and 45 years old with gestational age between 18 and 24 weeks. They attended antenatal care at the maternal-fetal medicine (MFM) unit at Bhumibol Adulyadej Hospital (BAH) between February and December 2022. The present study was approved by the BAH Ethics Committee (IRB number 113/64). The clinical trial registered number was TCTR20220105001.

Participants were informed about the study objectives (Figure 1). The informed consents were then taken from all participants. From the pilot study, mean (± standard deviation) of study and control group were 1.26±0.14 and 1.20±0.23, respectively. Alpha and beta errors were set at a level of 0.05 and 0.1 for the present study. Sample size was at least 249 cases per group by using Stata, version 12 (StataCorp LP, College Station, TX, USA). A total sample size of 525 cases was needed after the addition of 5% compensation. Pregnant woman older than 18 years old with singleton and accurate gestational age were recruited into the study. Accurate gestational age was calculated from the reliable last menstrual period or the parameters of first trimester ultrasound.

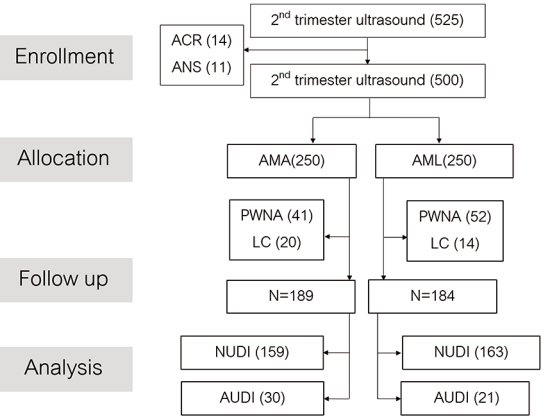


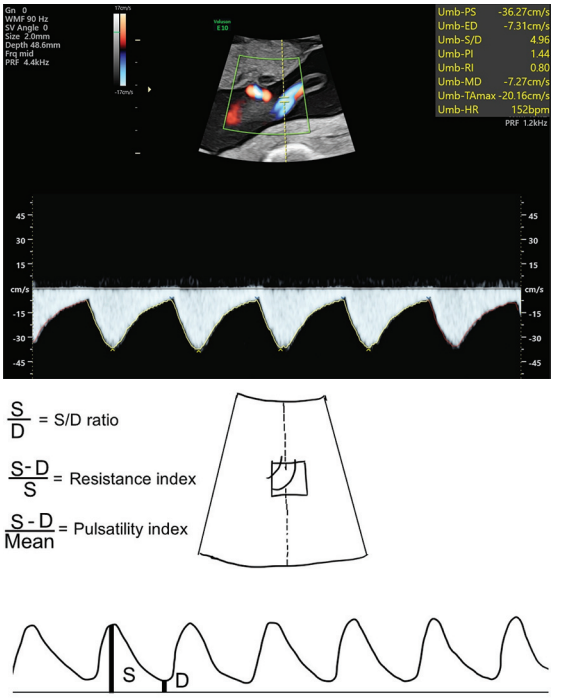
Figure 1. Flow chart of UDI study among AMA and MAL.

UDI=umbilical artery Doppler indices; AMA=advanced maternal age (≥35years); MAL=maternal age less than 35 years; ACR=abnormal chromosome; ANS=abnormal anatomical structure; PWNA=placental weight unavailable; LC=loss contact; NUDI=abnormal umbilical artery Doppler indices; AUDI=abnormal umbilical artery Doppler indices

Exclusion occurred with one or more of the following, abnormal structures of the placenta, umbilical cord, medical conditions affecting maternal vasculature, namely systemic lupus erythematosus (SLE), chronic kidney diseases, chronic hypertension (CHT), diabetes mellitus (DM), and smoking. Participants whose fetuses had abnormal chromosomes or abnormal anatomical structures were also excluded.

All participants were subjected to routine ultrasonographic study for the estimation of fetal weight, anomaly scan, placental placement site, and amniotic fluid volume estimation. Doppler ultrasound assessment was performed by a group of certified attending physicians and fellow at the MFM unit. Umbilical artery waveform was obtained by using color Doppler ultrasound mode (Voluson E10, GE, MA, USA) with RAB 4-8 L probe.

The technique for acquiring UDI was standardized across the site based on the technique issued by ISUOG 2021[23]. All three parameters of UDI were obtained as (Figure 2), 1) a sample was taken from a free-floating loop of the umbilical cord, 2) the examiner needed to make sure that the fetus was in a quiescence state, 3) venous signal needed to



This Doppler ultrasonography display the peak systolic and diastolic ratio (S=peak systolic velocity, D=end diastolic velocity). The time average mean velocity is obtained from calculation by computer-digitalized waveforms.

Figure 2. Ultrasonography image demonstrating the measurement of all umbilical artery Doppler indices.

be avoided, 4) the box of umbilical artery, at no less than 30 degree, was zoomed in, 5) the sweep speed used was 4 to 6 waveforms, 6) the velocity scale used was approximately 75% of the peak systolic velocity, 7) adjustment of pulse repetition frequency and color gain correction was done, 8) three waveforms were used in analyses of the UA-PI, UA-RI, and UA-S/D ratio. Pregnancy with vascular complication, smoking mother, and abnormal ultrasound finding such as fetal structural abnormality and abnormal placental or umbilical cord were excluded (Figure 1). All ultrasound measurements were processed in viewpoint 6 program (version 6.11, GE Healthcare GmbH). Any pregnancy with abnormal UDI was then referred to the high-risk pregnancy antenatal care clinic, BAH for a following work up.

Obstetric and neonatal outcomes, namely gestational age at delivery, route of delivery, placental width, placental weight, umbilical length, estimate blood loss, route of delivery, fetal gender, SGA, large for gestational age (LGA), low birth weight (LBW), presentation of placenta adherents, preterm labor, premature rupture of membrane (PROM), PIH, GDM, neonatal weight, Apgar score at 0, 5, and 10 minutes, fetal distress, admission and length of neonatal intensive care unit (NICU), stillbirth, and neonatal death were recorded for further analyses, The p-value of less than 0.05 was considered significant. Statistical analyses were carried out using the IBM SPSS Statistics, version 16.0 (IBM Corp., Armonk, NY, USA).

Demographic data were determined using frequency and percentage for categorical data while mean, standard deviation, median and interquartile range were used for continuous data. Comparisons between groups were performed using independent t-test, Mann-Whitney U test, chi-square test or Fisher's exact test as appropriate. Multivariable analysis by multiple logistic regression was used in determining independent risk factors, adjusting for potential confounders. The discrimination ability and optimal cutoff value of the UA index were determined by receiver operating characteristic (ROC) curve analysis. The level of statistical significance was set at $p<0.05$.

Results

Five hundred pregnant participants were recruited to the MFM unit for ultrasonography for anomaly screening at gestational age 18 to 24 weeks. The comparison of demographic data between pregnancies with advanced age, the study group, and normal age women, the control group, are shown in Table 1. The mean ages of the participants in the study and control groups were statistically different at 37.9±2.47 versus 26.0±4.47 years ($p<0.001$). Less than half of the study group had nulliparity at 23.2% versus 58.4% ($p<0.001$). The body mass index (BMI) of the study group was significantly greater than that of the control group at 25.08±5.25 versus 22.95±5.11 kg/m² ($p<0.001$). Both groups had comparable diastolic and systolic blood pressure as shown in Table 1.

All UA-PI, UA-RI, and UA-S/D ratios in the study group were significantly higher than those of the control group. The average UA-PI, UA-RI, and UA-S/D ratios of the study and the control groups were 1.33±0.21, 0.77±0.10, 4.24±0.98 and 1.27±0.22, 0.74±0.09, 3.95±0.97, respectively.

Data gathered from the labor and delivery records found that AMA parturients had higher incidence of GDM at 29.6 and 11.5% ($p<0.001$), PIH at 4.8 and 1.1% ($p<0.034$), and LGA at 12.2 and 5.8% ($p<0.015$). After delivery, neonates from both groups had similar rates of NICU admission, APGAR score, neonatal weight, and placental weight. In comparison

Table 1. Characteristics and outcome of pregnant women who had age less than 35 years old (control) and equal or more than 35 years old (study) with 250 cases per group

	Study (n=250)	Control (n=250)	p-value
Age (years); mean±SD	37.90±2.47	25.97±4.47	<0.001
BMI (kg/m^2); mean±SD	25.08±5.25	22.95±5.11	<0.001
SBP (mmHg); mean±SD	116.95±10.58	115.76±10.51	0.419
DBP (mmHg); mean±SD	72.46±9.12	71.16±8.93	0.106
EFW (g); mean±SD	382.44±135.27	397.38±108.99	0.176
Nulliparity; n (%)	58 (23.2)	146 (58.4)	<0.001
GA at study (weeks); mean±SD	20.52±1.88	20.84±1.61	0.057
UA-PI; mean±SD	1.33±0.21	1.27±0.22	0.001
UA-RI; mean±SD	0.77±0.10	0.74±0.09	0.001
UA-S/D ratio; mean±SD	4.24±0.98	3.95±0.97	0.001
GDM; n (%)	55 (29.6)	21 (11.5)	<0.001
GA at delivery (weeks); mean±SD	37.90±1.58	38.20±1.50	0.049
Vaginal delivery; n (%)	80 (43)	110 (60.1)	0.001
LGA; n (%)	29 (12.2)	14 (5.8)	0.015
PIH; n (%)	9 (4.8)	2 (1.1)	0.034
NICU admission; n (%)	17 (7.2)	10 (4.3)	0.234
NICU LOS (day); median (IQR)	8 (2 to 12.5)	6.5 (4 to 7)	0.853
APGAR at 5 minutes <7; n (%)	2 (0.9)	0 (0.0)	0.244
Clear meconium; n (%)	166 (91.2)	169 (92.9)	0.33
Male fetus; n (%)	103 (55.4)	93 (51.1)	0.411
Baby height; mean±SD	50.88±2.99	51.05±2.86	0.750
BHC (cm); mean±SD	33.31±1.70	33.07±1.71	0.055
BBC (cm); mean±SD	32.41±2.20	32.30±2.06	0.660
Placental weight (g); mean±SD	619.52±132.70	604.50±114.83	0.092

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; EFW=estimation of fetal weight; GA=gestational age; UA-PI=umbilical arterial pulsatility index; UA-RI=umbilical arterial resistance index; UA-S/D=umbilical arterial systolic/diastolic; GDM=gestational diabetes mellitus; LGA=large for gestational age; PIH=pregnancy induced hypertension; NICU=neonatal intensive care unit; LOS=length of stay; BHC=baby head circumference; BBC=baby burst circumference; SD=standard deviation; IQR=interquartile range

At delivery study (n=189) and control (n=184)

to the control group, the gestational age at delivery of the AMA group was significantly lower. However, there was no difference in fetal clinical outcomes among both groups.

The multivariable analysis was used to minimize the confounding factors such as BMI and gravida (Table 2). The analysis found that the study group had significantly higher values in all parameters. Table 3 shows the comparison between the current with the previous studies. The median and interquartile range of UA-PI, UA-RI, and UA-S/D ratio for the study and the control group are shown in Figure 3.

Discussion

From the present study, pregnant women with AMA had higher UA-PI, UA-RI, and UA-S/D ratios than the normal age group. The result differed from the UA-PI study by Erkamp in 2020. The mean UA-PI from the present study is 1.33 whereas Erkamp's study is 1.2 (Table 3). The present study examined UDI in the advanced and the normal age pregnant women, which were different from the previous study.

Participants in both groups of the present study were overweight based on the official guidelines set by the Thai Ministry of Health as a BMI of 23 kg/m² or above is considered overweight.

The BMI of AMA group was statistically higher than that of the control group. Overweight mothers are more likely to have sluggish blood flow and undesirable lipid profiles. Given that blood viscosity is influenced by BMI, it is not surprising that all UDI, including UA-PI, UA-RI, and UA-S/D ratio, are all slightly higher in mothers with advanced age[24].

The BMI of the participants in the present study had BMI higher than those of Erkamp's study participants at 25.3 versus 24.76 kg/m², respectively. The subjects in the previous study, however, were

Table 2. Multiple logistic regression analysis for comparison of umbilical artery Doppler indices during the second trimester of pregnant women who had age less than 35 years old (control) and equal or more than 35 years old (study)

	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
UA-PI	3.820	1.660 to 8.791	0.002	3.596	1.421 to 9.101	0.007
UA-RI	36.062	3.753 to 346.484	0.002	14.738	1.184 to 183.385	0.036
UA-S/D ratio	1.364	1.133 to 1.643	0.001	1.138	1.071 to 1.622	0.009

UA-PI=umbilical arterial pulsatility index; UA-RI=umbilical arterial resistance index; UA-S/D=umbilical arterial systolic/diastolic; OR=odds ratio; CI=confidence interval

Adjusted OR for body mass index, gestational age, nulliparity and abortion

Table 3. Comparison of characteristic of umbilical artery Doppler indices measurement

	Present		Erkamp et al.		Drukker et al.	Paco et al.	Cooley et al.
Year	2023		2020		2020	2014	2011
Country	Thailand		Netherland		U.K.	Spain	Ireland
Age (years)	37.90	25.97	29.7		28.9	32	26.3
	≥35	<35	≥35	<35			
Number	250	250	7035	1241	431	4565	1122
BMI (kg/m^2)	25.25	22.95	24.76	25.16	23.9		
GA (weeks)	20.52	20.84	20.5			20.5	
Nulliparity (%)	23.2	58.4	59.2	33.8	60		
SBP (mmHg)	116.95	115.76					
DBP (mmHg)	72.46	71.16					
EFW at study (g)	382	397					
UA-PI	1.33	1.27	1.2	1.17	1.1	1.2	1.32
UA-RI	0.77	0.74			0.69		
UA-S/D ratio	4.24	3.95			3.23		
GA at delivery	37.90	38.20					
BW (kg)	3.09	3.04	3.4	3.5		3.3	
SGA (%)	8.8	12.69					
Placental weight	619.52	604.50					
FPR	4.93	5.10					
P/B ratio	0.207	1.99					

BMI=body mass index; GA=gestational age; SBP=systolic blood pressure; DBP=diastolic blood pressure; EFW=estimation of fetal weight; UA-PI=umbilical arterial pulsatility index; UA-RI=umbilical arterial resistance index; UA-S/D=umbilical arterial systolic/diastolic; SGA=small for gestational age; FPR=fetoplacental ratio; P/B ratio=placenta/birth weight ratio

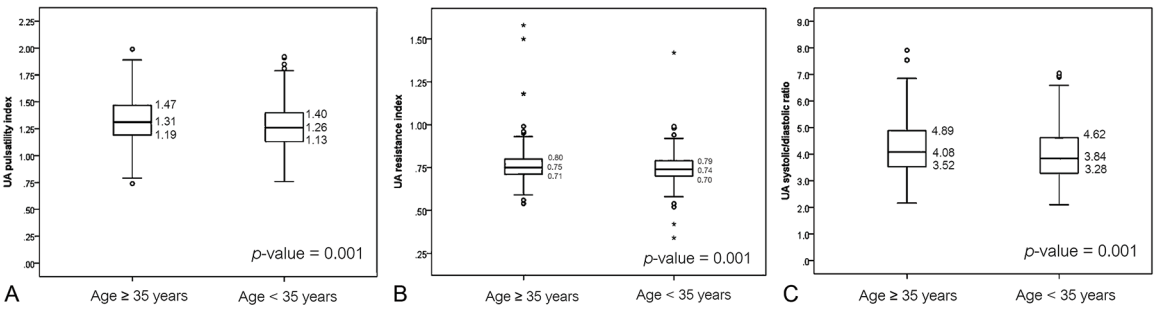


Figure 3. (A) A boxplot comparing the distribution of umbilical artery (UA) pulsatile index between advanced maternal age parturient and parturient age less than 35 years old. (B) A boxplot comparing the distribution of umbilical artery (UA) resistance index between advanced maternal age parturient and parturient age less than 35 years old. (C) A boxplot comparing the distribution of umbilical artery (UA) systolic to diastolic ratio between advanced maternal age parturient and parturient age less than 35 years old.

regarded to have a normal BMI by Caucasian's standard with a BMI of 25 kg/m² or above is considered overweight.

Similarly, both previous and current studies found that the average UA-PI of AMA patients was higher than that of normal age patients. It is evident that older pregnant women are more likely to experience unfavorable fetal outcomes, possibly as a result of an increase in BMI with advancing age.

Principal investigator also noticed 29.6% and 11.5% of AMA and maternal age less than (MAL) mothers with GDM at birth with statistical significance. All findings pointed out that AMA mothers are prone to undesirable lipid/sugar profile, which eventually could show up in UDI index measurement. Nutritional counseling and exercise might be required and implemented early in this mother group to lessen the chance of undesirable UDI outcome thus lower undesirable fetal outcome in later trimester.

From Table 2, the values of the UA-RI, UA-PI, and UA-S/D ratio are affected in the same manner. Reduction of diastolic blood pressure in the umbilical artery increases the UA-RI, UA-PI, and UA-S/D ratio. From the current study, the adjusted odds ratio of UA-RI, UA-PI, and UA-S/D ratio is 14.73, 3.6, and 1.1, respectively. As a result, UA-RI ought to be a more accurate prognostic indicator than UA-PI and UA-S/D[12,15,17].

Outcome from the present study showed a higher number of poor perinatal outcomes of AMA such as LGA, PIH, or GDM with statistical significance. It is too early to conclude that UA-RI, UA-PI, and UA-S/D ratio could predict the mentioned perinatal outcome. However, the results are in lieu of the previous literature[5-9,21,25].

The present study's finding is consistent with the normal ratio of birth weight to placental weight, which is about 5. There is no difference in the ratio between the study and the control groups (Figure 4). In the present study, birth weight and placental weight ratio might not represent FGR in the same conclusion of Salavati's work[26].

The strength of the present study was that all three values of UDI were measured. In addition, the outcome advanced until delivery. Moreover, participants were all singleton pregnant woman who were non-smokers and had no underlying diseases that would have affected their vasculatures. However, the limitation was that confounding factors such as BMI or parity, especially for AMA, could not be avoided.

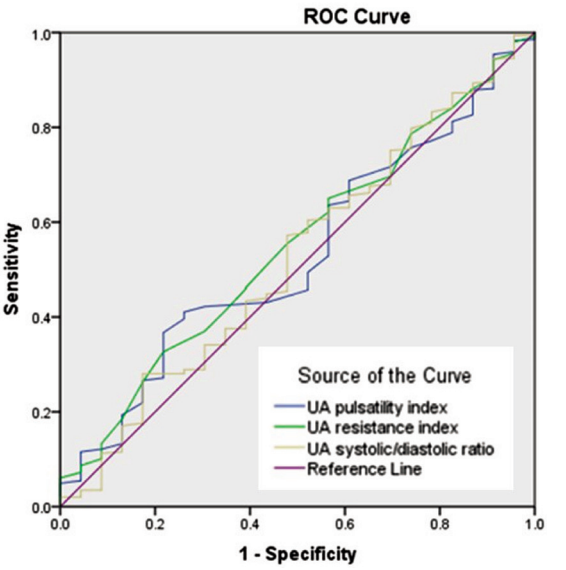


Figure 4. ROC curve of UDI and BW/PW ratio >5 (n=369).

ROC=receiver operating characteristic curve; UDI=umbilical artery Doppler indices; BW/PW ratio=birth weight/placental weight ratio

Conclusion

In conclusion, AMA pregnant women had higher UA-PI, UA-RI, and S/D ratio than those younger than 35 years old. Among AMA pregnant women, there were high rates of cesarean delivery, LGA, PIH, and GDM. The authors suggest that use of UA-RI is a more powerful factor for perinatal outcome prediction. However, more studies are needed.

What is already known on this topic?

AMA pregnant women had higher UA-PI, UA-RI, and S/D ratio than those who were younger than 35 years old. High rates of cesarean delivery, LGA, PIH, and GDM were found among AMA pregnant women.

What this study adds?

UA-RI is a more accurate prognostic factor for perinatal outcome prediction.

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Conflicts of interest

The authors declare no conflict of interest.

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