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MATERNAL-FETAL MEDICINE

# Trends and risk factors of stillbirth in Taiwan 2006–2013: a population-based study

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## Abstract

**Purpose** To examine temporal trends in stillbirth and its associated risk factors in Taiwan.

**Methods** This was a population-based cohort study. Data were extracted from the Birth Certificate Application database. Singleton births at 28 or more gestational weeks were included. A total of 1,536,796 births, including 3741 stillbirths, were analyzed from January 2006 to December 2013.

**Results** The stillbirth rate was 2.4 per 1000 births and there was no change in the stillbirth rate during the study period. The adjusted odds ratio (aOR) for stillbirth was 1.28 for maternal age between 35 and 40 years and 1.79 for maternal age ≥ 41 years, with 21–34 years as the reference. The risk for stillbirth increased in single women (aOR, 2.4), female baby (aOR, 1.08), small for gestational age (aOR, 6.34) and large for gestational age (aOR, 1.52) infants, and women with hypertension (aOR, 3.78), diabetes mellitus (aOR, 2.04), anemia (aOR, 1.65), and oligohydramnios or polyhydramnios (aOR, 2.46).Women with heart disease and maternal age ≤ 20 years had no significant association with stillbirth after adjusting for various risk factors.

**Conclusions** Although the rate of stillbirth was stable during the study period, the incidence of risk factors associated with stillbirth, such as advanced maternal age, hypertension, diabetes mellitus, and anemia, had increased over time. Understanding about the risk factors might change protocols and allow for earlier detection of problems and prevention of stillbirths. Prevention or management of risk factors should be undertaken to reduce stillbirth rate.

**Keywords** Stillbirth · Trends · Risk factors · Third trimester

## Introduction

Stillbirth is the worst possible birth outcome and the stillbirth rate is an indicator of the quality of antenatal and intrapartum care [1]. The World Health Organization (WHO) defines stillbirth as a baby born with no signs of life at or after 28 weeks' gestation. In 2015, a global stillbirth rate estimate was 18.4 per 1000 births and this varied according to the country. Developed countries showed a lower stillbirth rate at 3.5 per 1000 total births while sub-Saharan Africa and Southern Asia had the highest rates of stillbirth ranging between 25.5 and 28.7 per 1000 total births. In 2009, an estimated 2.6 million babies were stillborn in the third trimester worldwide [2]. Loss of an expected baby is a tragedy and can have long-lasting psychological impacts on women and their families. Therefore, identifying contributing factors can facilitate the development of preventive strategies.

A recent study was conducted to investigate the factors associated with late fetal death. This study noted

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prematurity, low birth weight, macrosomia, and sociodemographic factors such as inadequate maternal preparation, mothers of African origin, maternal age greater than 35 years, and single mothers to be associated factors. This study also indicated that the rate of late fetal mortality in Spain in 2015 had not decreased when compared with that in 2010 [3]. Hu et al. [4] reported that the overall stillbirth rate occurring after 20 weeks gestation between 2001 and 2004 in Taiwan was 9 per 1000 births. Risk factors associated with stillbirth included advanced maternal age, teenage pregnancy, multiple gestations, maternal medical disease during pregnancy, and intrapartum obstetric complications; however, these factors were not corrected for other demographic data, and there is a lack of a comprehensive model to predict stillbirth in Taiwan [4].

In the Every Women Every Child project, prioritization of the prevention of stillbirths post2015 involved attenuating preventable maternal, newborn, and child deaths, and stillbirths [5]. Improvement in the understanding of the causes and predictors of stillbirth is crucial to achieve the new worldwide goal for maternal and child health [6]. There is a paucity of up-to-date information on the trend in stillbirths in singleton pregnancies over time. An understanding of the risk factors will assist in improving clinical outcomes. In this population-based cohort study, we examined the trends of stillbirth in Taiwan from 2006 to 2013, compared stillbirth rates during the study period, and assessed the associated maternal risk factors.

## Methods

The data for this study were extracted from the Birth Certificate Application (BCA), Ministry of Health and Welfare, Taiwan, between January 1, 2006 and December 31, 2013. According to the law, all births in Taiwan must be registered within 7 days following delivery by the birth attendants. Owing to mandatory and online input, the database is complete and reliable. A validation study for the BCA showed a low rate of missing information and high level of validity [7]. The database contains data for babies born at more than 20 completed weeks of gestation and includes information regarding all live births and stillbirths, maternal demographic characteristics, reproductive history, birth characteristics of newborns, and medical complications.

To eliminate potentially confounding factors, we excluded congenital anomalies ($n=7827$, 0.5%), as they significantly contribute to the stillbirth rate and there is no effective prevention for them. Moreover, an increasing rate of prenatal screening has led to an increase in the number of terminations performed in the recent decades [8]. Multiple gestations ($n=47{,}666$, 3%) were also excluded as the BCA dataset presents each birth record individually and has multiple birth records for one mother. Only non-anomalous and singleton pregnancies where delivery occurred between 28 and 42 weeks of gestation were included.

Variables were chosen based on their known clinical relevance and from previous publications [4, 8] and included maternal characteristics, newborn characteristics, and maternal medical complications. Gestational age was determined based on maternal date of last menstruation or using ultrasound examination. Newborn body weight was divided into three categories based on an international fetal growth and sex-specific standard [9]. Small for gestational age (SGA) newborns were identified as having birth weights below the 10th percentile for gestational age, appropriate for gestational age (AGA) newborns were defined as having birth weights between the 10th and 90th percentiles (inclusive) for gestational age, and large for gestational age (LGA) newborns were defined as having birth weights above the 90th percentile for gestational age. Medical complications included diabetes mellitus (pre-existing or gestational), anemia, heart disease, hypertension (pre-existing or pregnancy-induced), and oligohydramnios or polyhydramnios. Maternal characteristics included age, marital status, and original nationality. Maternal age was divided into four groups: younger ($\leq 20$), normal (21–35), advanced (36–40), and very advanced ($\geq 41$) years old. During the past 20 years, female married immigrants have steadily increased, mainly in southeastern Asia and mainland China; therefore, original maternal nationality was categorized as foreign and native.

Chi-square test for trend was used to compare the difference in stillbirth rates and maternal characteristics over the period of eight years. Adjusted standardized residuals (ASRs) were used to identify groups with significant differences. A residual greater than 2.0 was taken to indicate a significantly higher frequency, and a residual less than – 2.0 was considered to indicate a significantly lower frequency. Univariate analyzes to evaluate associations between individual risk factors and stillbirth incidence were performed using the logistic regression analysis for dichotomous variables. Variables with statistically significant association on univariate analysis were included in a multivariable binary logistic regression model. We used logistic regression analysis to examine the adjusted effects of various risk factors on stillbirth. Results are reported as adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs). All factors were analyzed with $\alpha = 0.05$ and $P \leq 0.05$ was regarded as significant. Statistical analyzes were performed using the SPSS software package version 22.0 (IBM Corporation, Chicago, IL, USA).

## Results

A total of 1,536,796 births between 2006 and 2013 were included in the analysis, of which 3741 (2.43‰) were stillbirths. The number and proportion of stillbirths and the maternal characteristics over the study period are indicated in Table 1. Results indicate that there was no change in the stillbirth rate during the study period ($\chi^2 = 0.907$, $p = 0.341$). The stillbirth rate was 2.59‰ in 2006 and 2.4‰ in 2013.

**Table 1** Number of live birth and stillbirth in Taiwan from 2006 to 2013

| Year | Number of lived birth | Number of stillbirth | Stillbirth rate (‰) | Total numbers |
|---|---|---|---|---|
| 2006 | 198,017 | 515 | 2.59 | 198,532 |
| 2007 | 196,035 | 464 | 2.36 | 196,499 |
| 2008 | 189,552 | 492 | 2.59 | 190,044 |
| 2009 | 185,685 | 427 | 2.29 | 186,112 |
| 2010 | 160,100 | 364 | 2.27 | 160,464 |
| 2011 | 190,729 | 489 | 2.56 | 191,218 |
| 2012 | 225,201 | 539 | 2.39 | 225,740 |
| 2013 | 187,736 | 451 | 2.4 | 188,187 |
| Total | 1,533,055 | 3,741 | 2.43 | 1,536,796 |

### Maternal demographic characteristics

Table 2 shows the maternal demographic and infant characteristics across the study period. The mean maternal age increased from 29.10 years in 2006 to 31.30 years in 2013 ($p < 0.001$). There was a significant increase in the proportion of mothers with advanced maternal age in Taiwan ($p < 0.001$); births at maternal age 35–40 years increased from 7.3% in 2006 to 14.3% in 2013 and at more than 41 years also increased from 0.7% in 2006 to 1.6% in 2013. There was a decrease in foreigner and single women deliveries in comparison to those of Taiwanese origin and married women. Foreigner women deliveries in Taiwan decreased from 12.1% in 2006 to 6.9% in 2013 ($p < 0.001$), while single women deliveries in Taiwan reduced from 6.6% in 2006 to 5.9% in 2013 ($p < 0.001$).

### Characteristics of the infants

The proportion of male babies was 52.1% overall while that for female babies was 47.9% over the study period. The percentage of female babies significantly increased from 47.7% in 2006 to 48.2% in 2013 ($p < 0.001$). An increasing proportion of AGA and SGA infants over the study period was observed. The proportion of SGA infants was 6.5% overall and increased from 6.5% in 2006 to 6.8% in 2013.

**Table 2** Percentage of maternal characteristics in Taiwan from 2006 to 2013 ($n = 1,536,796$)

| Maternal demographic characteristics | 2006–2013 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| Maternal age, years | | | | | | | | | | |
| Mean | 30.28 | 29.10 | 29.47 | 29.80 | 30.16 | 30.57 | 30.83 | 31.01 | 31.30 | < 0.001 |
| ≤ 20 | 3.0 | 4.5* | 3.6* | 3.2* | 2.8* | 2.9* | 2.4* | 2.2* | 2.5* | < 0.001 |
| 21–34 | 85.7 | 87.4* | 87.6* | 87.2* | 86.8* | 84.8* | 85.1* | 84.6* | 81.5* | |
| 35–40 | 10.2 | 7.3* | 8.0* | 8.7* | 9.4* | 11.1* | 11.2* | 11.9* | 14.3* | |
| ≥ 41 | 1.1 | 0.7* | 0.8* | 0.9* | 1.0* | 1.2* | 1.2* | 1.4* | 1.6* | |
| Ethnic origin | | | | | | | | | | |
| Taiwan | 91 | 87.9* | 89.4* | 90.1* | 91.1* | 91.2* | 92.3* | 92.6* | 93.1* | < 0.001 |
| Foreign | 9 | 12.1* | 10.6* | 9.9* | 8.9* | 8.8* | 7.7* | 7.4* | 6.9* | |
| Marital status | | | | | | | | | | |
| Single | 6.1 | 6.6* | 6.6* | 6.3* | 5.8* | 6.7* | 5.6* | 5.3* | 5.9* | < 0.001 |
| Married | 93.9 | 93.4* | 93.4* | 93.7* | 94.2* | 93.3* | 94.4* | 94.7* | 94.1* | |
| Baby sex | | | | | | | | | | |
| Male | 52.1 | 52.3* | 52.3* | 52.3* | 52.0 | 52.1 | 51.9 | 51.8* | 51.8* | < 0.001 |
| Female | 47.9 | 47.7* | 47.7* | 47.7* | 48.0 | 47.9 | 48.1 | 48.2* | 48.2* | |
| Baby bodyweight | | | | | | | | | | |
| SGA | 6.5 | 6.5 | 6.4 | 6.2* | 6.4 | 6.5 | 6.5 | 6.5 | 6.8* | < 0.001 |
| AGA | 85.8 | 85.3* | 85.6* | 85.7 | 85.9 | 85.8 | 85.9 | 86.1* | 86.2* | |
| LGA | 7.7 | 8.2* | 8.0* | 8.2* | 7.7 | 7.8 | 7.6* | 7.5* | 7.0* | |

*SGA* Small for gestational age, *AGA* Appropriate for gestational age, *LGA* Large for gestational age

*Adjusted standardized residual ≤ – 2 or ≥ 2

Additionally, the proportion of AGA infants was 85.8% overall and increased from 85.3% in 2006 to 86.2% in 2013. With regard to LGA, a decreasing trend in proportion was noted. The proportion of LGA infants was 7.7% overall and reduced from 8.2% in 2006 to 7.0% in 2013 ($p < 0.001$).

## Medical complications

Table 3 shows the maternal medical complications over the study period. An increasing proportion of mothers with hypertension, DM, and anemia over the study period was observed. The proportion of mothers with hypertension was 1.12% overall and increased from 1.11% in 2006 to 1.30% in 2013 ($p < 0.001$). Additionally, the proportion of mothers with DM was 0.94% overall and increased from 0.69% in 2006 to 1.57% in 2013 ($p < 0.001$) and the proportion of mothers with anemia was 0.83% overall and increased from 0.78% in 2006 to 1.05% in 2013 ($p < 0.001$). With regard to women with abnormality of amniotic fluid and heart disease, a decreasing trend in proportion was noted. The proportion of mothers with oligohydramnios or polyhydramnios was 0.19% overall and reduced from 0.2% in 2006 to 0.17% in 2013 ($p < 0.001$), and that of mothers with heart disease was 0.22% overall and decreased from 0.25% in 2006 to 0.21% in 2013 ($p < 0.001$).

## Variables associated with stillbirth

The results of univariate and multivariable binary logistic regression analysis for stillbirth are shown in Table 4. For demographic variables, the crude OR values showed an increased risk of stillbirth in women up to 35 years of age, women less than 20 years of age, and single women. Among the obstetric variables considered in the study, there was

**Table 3** Incidence rate (%) of maternal medical complications in Taiwan from 2006 to 2013 ($n = 1{,}536{,}796$)

| Maternal medical complications | 2006–2013 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | *P* |
|---|---|---|---|---|---|---|---|---|---|---|
| Hypertension | 1.12 | 1.11 | 1.03* | 1.02* | 1.11 | 1.14 | 1.17 | 1.13 | 1.30* | < 0.001 |
| DM | 0.94 | 0.69* | 0.68* | 0.72* | 0.81* | 0.97 | 0.97 | 1.09* | 1.57* | < 0.001 |
| Anemia | 0.83 | 0.78* | 0.76* | 0.7* | 0.69* | 0.81 | 0.89* | 0.93* | 1.05* | < 0.001 |
| Heart disease | 0.22 | 0.25* | 0.23 | 0.24* | 0.21 | 0.23 | 0.21 | 0.16* | 0.21 | < 0.001 |
| Oligohydramnios/polyhydramnios | 0.19 | 0.20 | 0.21* | 0.19 | 0.208 | 0.22* | 0.19 | 0.17* | 0.17* | < 0.001 |

*DM* Diabetes mellitus

*Adjusted standardized residual ≤ – 2 or ≥ 2

**Table 4** Associated factors related to stillbirth (logistic regression)

| Variables | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P* value | Adjusted OR (95% CI) | *P* value |
| Maternal age | | | | |
| ≤ 20 | 1.39 (1.18–1.64) | < 0.001 | 0.91 (0.77–1.08) | 0.301 |
| 21–34 | Reference | | Reference | |
| 35–40 | 1.38 (1.26–1.52) | < 0.001 | 1.28 (1.16–1.41) | < 0.001 |
| ≥ 41 | 2.31 (1.87–2.86) | < 0.001 | 1.79 (1.45–2.22) | < 0.001 |
| Taiwanese origin | 1.07 (0.95–1.20) | 0.283 | NA | |
| Female Newborn | 1.13 (1.06–1.20) | < 0.001 | 1.08 (1.01–1.15) | 0.022 |
| Gestational-age weight | | | | |
| SGA | 7.19 (6.70–7.72) | < 0.001 | 6.34(5.89–6.81) | < 0.001 |
| AGA | Reference | | Reference | |
| LGA | 1.65 (1.47–1.85) | < 0.001 | 1.52 (1.36–1.71) | < 0.001 |
| Single | 2.80 (2.56–3.06) | < 0.001 | 2.40 (2.19–2.63) | < 0.001 |
| Hypertension | 7.22 (6.39–8.16) | < 0.001 | 3.78 (3.32–4.31) | < 0.001 |
| DM | 3.07 (2.53–3.73) | < 0.001 | 2.04 (1.67–2.51) | < 0.001 |
| Anemia | 1.96 (1.52–2.53) | < 0.001 | 1.65 (1.27–2.14) | < 0.001 |
| Heart disease | 1.99 (1.21–3.25) | 0.006 | 1.03 (0.62–1.69) | 0.916 |
| Oligohydramnios/polyhydramnios | 6.51 (4.86–8.72) | < 0.001 | 2.46 (1.82–3.33) | < 0.001 |

*OR* Odds ratio, *CI* Confidence interval, *DM* Diabetes mellitus, *NA* Not applicable, *SGA* Small for gestational age, *AGA* Appropriate for gestational age, *LGA* Large for gestational age

an increased risk of stillbirth in women with SGA or LGA, hypertension, DM, anemia, oligohydramnios or polyhydramnios, and heart disease. Rate of stillbirth in foreign women was not different from that in mothers of Taiwanese origin ($p = 0.283$).

The multivariate logistic regression analysis revealed a significantly increased risk of stillbirth with maternal age from 35–40 years (aOR 1.28, 95% CI 1.16–1.41, $p < 0.001$), maternal age ≥ 41 years (aOR 1.79, 95% CI 1.45–2.22, $p < 0.001$), single women (aOR 2.40, 95% CI 2.19–2.63, $p < 0.001$), female newborn (aOR 1.08, 95% CI 1.01–1.15, $p = 0.022$), SGA (aOR 6.34, 95% CI 5.89–6.81, $p < 0.001$), LGA (aOR 1.52, 95% CI 1.36–1.71, $p < 0.001$), women with hypertension (aOR 3.78, 95% CI 3.32–4.31, $p < 0.001$), DM (aOR 2.04, 95% CI 1.67–2.51, $p < 0.001$), anemia (aOR 1.65, 95% CI 1.27–2.14, $p < 0.001$), and oligohydramnios or polyhydramnios (aOR 2.46, 95% CI 1.82–3.33, $p < 0.001$). Women with heart disease had no significant association with stillbirth after adjusting for various risk factors. Also, maternal age less than 20 years had a similar stillbirth rate compared with that at 21–35 years.

## Discussion

### Main findings

This study examined trends in singleton stillbirth and its associated risk factors in Taiwan using a nationwide population-based dataset between 2006 and 2013. Our study found that the rate of stillbirth did not change over time and its risk factors were advanced maternal age, single women, female fetuses, inappropriate birth weight for gestational age, and women with hypertension, DM, anemia, abnormality in the volume of amniotic fluid, and heart disease. Although the rate of stillbirth was stable during the study period, the incidence of maternal medical complications had increased over time. According to a recent report, the incidence of preeclampsia has increased in Taiwan from 2001 to 2014 [10]. Our study also found that the proportion of mothers with hypertension, DM, and anemia has increased over the past years. These changes are likely related to different screening and diagnostic tests for gestational diabetes mellitus (GDM) were used during the study periods. Many hospitals in Taiwan adopted the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria instead of the American College of Obstetrician and Gynecologists (ACOG)'s two-step approach. For instance, Chang Gung Memorial Hospital, Taiwan's largest health care provider, adopted the IADPSG recommendations from July 2011. Studies showed that the incidence of GDM increased when using the IADPSG criteria compared to that using the two-step method [11]. O'Sullivan et al. also found that women who were diagnosed as having normal glucose tolerance using the WHO criteria but diagnosed with GDM using the IADPSG criteria had a significantly greater risk of gestational hypertension and preeclampsia compared to that in the women diagnosed with normal glucose tolerance using the IADPSG criteria [12]. Overall, the results of this study might contribute to improving the management approaches for high risk pregnancies in Taiwan.

### Interpretation

Our findings were consistent with that of previous studies, which showed that advanced maternal age was a risk factor for stillbirth [4, 13–17]. In addition, the higher the maternal age, the greater the risk for stillbirth. Younger maternal age was not found to be a statistically significant risk factor in this study, although it has been known to be one of the major risk factors for stillbirth [3, 17–20]. The increase in stillbirth risk with younger age is often attributed to the combined effect of poor nutrition, decreased access to prenatal care, lower socioeconomic status, and endocrine immaturity; the reason for the non-significant association noted in this study may be attributable to adjustments made for a number of known complications and the exclusion of newborns with congenital malformations.

The relationship between fetal sex and stillbirth is unclear from the results of previous studies. We observed an increasing trend for stillbirths in female fetuses compared with male fetuses during the study period. In contrast, Mondal et al. conducted a meta-analysis based on more than 30 million births from studies in various regions and reported a 10% elevated risk of stillbirth in male fetuses as compared with that in female fetuses [21]. Previous studies conducted in Taiwan found that there was no significant difference in the incidence of stillbirths between singleton male and female fetuses, but the incidence of stillbirths was significantly higher in males than in females among mothers with multiple gestations [4, 22]. The reason for a higher risk of stillbirths in females observed in our study remains unclear and continued observation in this regard is warranted.

This study revealed gradually reducing proportions of immigrant mothers from Southeast Asian countries and China. Foreign women had a similar stillbirth rate to that of Taiwanese women. Our finding is inconsistent with the data of previous studies showing that foreign women had a significantly lower stillbirth rate compared to Taiwanese women between 2001 and 2004 [4]. This change indicates that irrespective of the origin of the mother, the stillbirth rate has remained the same over time.

With regard to the weight of the baby, our study indicates that both SGA and LGA babies had a significant increase in stillbirth rate, which is consistent with the findings of previous studies [23]. This is comparable with the study

by Haruyama et al., who reported that SGA was associated with an increase in stillbirth rate, while LGA and AGA had a similar risk for stillbirth [24]. In addition, more recent reports have identified fetal growth restriction as one of the main contributors to stillbirth [25]. Since the incidence of SGA has increased, more research is needed to understand the causal relationship between SGA and stillbirths and its causes so that its incidence and effects can be reduced.

In relation to maternal medical complications, results consistent with those of previous studies were noted. Women with hypertension [4, 14, 24], DM [4, 26], anemia [4, 16], and abnormal amniotic fluid volume [4] have an increased risk for stillbirth. Further research should focus on early detection and management in such cases.

### Strengths and limitations

The main strengths of this study were the nationwide data collection and the large sample size. The nature of the study and its duration also enabled us to note trends according to time. However, this study has some limitations. On the one hand, causes for stillbirth may differ antenatally and intrapartum. The database source was limited with regard to outcome variables, for both live births and stillbirths. For newborn death within a few hours of delivery, most birth attendants only hand over the stillborn baby to the parents, instead of providing them with the death and birth certificates for their baby. While this may be less traumatic for the bereaved parents, it also makes it difficult to distinguish the risk factors from the causes of stillbirth. Additionally, some important demographic variables were lacking from the database such as parity, occupation, and number of prenatal visits. A recent report on risk factors for stillbirth in Japan had indicated that nulliparous women are at an increased risk for stillbirth [24].

## Conclusion

Altogether, the results of the present study indicate that the stillbirth rate in the third trimester in Taiwan has not changed despite an increasing incidence of risk factors in recent years between 2006 and 2013. The associated risk factors include maternal characteristics of advanced maternal age, single women, female fetuses, and SGA as well as LGA. Women with hypertension, DM, anemia, and abnormal amniotic fluid volume, either increased or decreased, were also found to have an increased risk for stillbirth. Our study may enhance our understanding of stillbirths and its associated factors and improve prevention or management strategies of risk factors so as to reduce the stillbirth rate.

## Ethical approval and informed consent

The study was approved by the Institutional Review Board of Cheng Hsin General Hospital and the review board waived the requirement of informed consent. This article does not contain any studies with human participants performed by any of the authors.

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**Author contributions** CCS: conceptualization, project administration and development, manuscript writing. HHC: methodology, resources manuscript writing. LLC: data management, data analysis, supervision manuscript review and editing.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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