Research

Impact of Inter-Pregnancy Interval on Long-Term Endo-Metabolic Health of the Offspring

Liron Seidman[1], Tamar Wainstock[2], Eyal Sheiner[3], Gali Pariente[4], Ruslan Sergienko[5], Asnat Walfisch[6]

[1]The Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
[2]Ben-Gurion University of the Negev, Department of Epidemiology and Health Services Evaluation, Beer-Sheva, Israel.
[3]Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
[4]Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
[5]Ben-Gurion University of the Negev, Department of Epidemiology and Health Services Evaluation, Beer-Sheva, Israel.
[6]Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

ABSTRACT

Background: Inter-pregnancy interval (IPI), defined as the time interval between a live birth and estimated conception time of a subsequent pregnancy, has an established effect on perinatal outcome. The long-term impact of IPI on offspring is unknown. This study aimed to examine the effect of short and long IPIs on long-term endo-metabolic health of offspring.
Subjects and Method: This population-based cohort study included singleton live births in parturient with at least one previous birth. Singleton deliveries between the years 1991-2014 in a regional tertiary medical center were included. Offspring were followed until 18 years of age for endo-metabolic related hospitalizations. Survival curves were used to compare cumulative incidence of endo-metabolic morbidity, and Cox proportional hazards models to control for confounders.
Results: During the study period 144,397 deliveries met the inclusion criteria. Offspring following long IPIs exhibited higher rates of endo-metabolic related hospitalizations. Survival cur-ve demonstrated a significantly higher cumulative incidence of endo-metabolic morbidity in the long IPI group (p<0.001). The Cox model demonstrated long IPI to significantly increase the risk for endo-metabolic related hospitalizations during childhood (aHR= 1.34, 95%CI= 1.06 to 1.70; p=0.015).
Conclusion: Long IPI appears to have an independent impact on long-term endo-metabolic health of the offspring.

Keywords: pregnancy interval, offspring, endocrine health, metabolic morbidity, obesity

Correspondence:
Liron Seidman. The Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev. Ben-Gurion University Medical School, Soroka University Medical Center, 151 IzakRager Ave, Be'er-Sheva 84101, Israel. Email: lironseidman@gmail.com. Mobile: +972-524215808

BACKGROUND

Interpregnancy interval (IPI) is the period between the birth of a live newborn and the conception of the next sibling (Class et al., 2017). Various definitions have been used to define IPI. One commonly used defini-

tion for "short IPI" refers to an interval of less than 18 months. Other researchers, however, have referred to a "short IPI" within a shorter range of less than three to six months (Li et al., 2018). There seems to be wide agreement regarding the definition of "long IPI," which is frequently defined as an IPI longer than 59 or 60 months (Conde-Agudelo et al., 2006).

The possible impact of IPI on perinatal outcomes has been investigated since the early 1920s (Li et al., 2018). A deviation from an average IPI length was shown to be associated with adverse outcomes in offspring. As IPI is a potentially modifiable risk factor, it attracted significant attention from the medical community (Li et al., 2018).

Both short and long IPIs have been reported to be associated with a significantly increased risk of adverse perinatal outcomes, such as preterm delivery (PTD), low birth weight (LBW<2500 g), small for gestational age (SGA) and perinatal death (Conde-Agudelo et al., 2006). For instance, Ratzon et al. (2011) showed that short IPI increases the risk of adverse pregnancy outcomes such as recurrent preterm delivery, and Class et al. (2017) found that long IPI increases the risk of PTD by 51%, the risk of LBW by 61%, and the incidence of SGA by 54%.

Studies suggest a difference in the direct influence of short or long IPIs. Short IPI associated adverse perinatal outcomes are largely attributed to familial confounding. The association of long IPI with infant morbidities has more often been suggested to be independent of measured and unmeasured confounding factors (Class et al., 2017).

It seems that little is currently known about the influence of IPI on long-term childhood growth, development and health. This stands in contrast with the current growing interest and numerous publications on perinatal exposures and their impact on long term health of offspring (Barker et al., 2002; De Boo and Harding, 2006).

Some investigators explored the impact of several pregnancy and maternal characteristics on the endo-metabolic health of their offspring (Paz Levy et al., 2017; Spiegel et al., 2019). Maternal characteristics include adverse early pregnancy lipid profile and increased pre-pregnancy body mass index (BMI) (Oostvogels et al., 2014; van Lieshout et al., 2017), as well as maternal diabetes or hypothyroidism (Abokaf et al., 2018; Eshkoli et al., 2019). Some authors suggested these exposures to elevate the risk of later offspring metabolic health (van Lieshout et al., 2017). Childhood obesity has become a significant world-wide epidemic with important social and health burdens (Tran et al., 2019). In light of the disturbing increase over the last decade in the incidence of endo-metabolic disorders in children, the authors decided to examine this association. Their aim was to examine the effect of short (<6 months) and long (>60 months) IPIs on long-term endo-metabolic health of the offspring in a large population-based cohort study.

SUBJECTS AND METHOD

1. Study Design

This population-based retrospective cohort study was conducted at the Soroka University Medical Center (SUMC), the sole tertiary medical center in the Negev (southern region of Israel). Thus, SUMC serves the entire population of the region, 750,000 inhabitants in 2018 (Bureau and Statistics, 2019). Since SUMC is the major medical center in the south of Israel, most of the children born at SUMC are expected to be hospitalized there, if the need arises.

2. Population and Sample

All singleton pregnancies of women who delivered at the SUMC and their infants (up to the age of 18 years) between January 1991 and January 2014. Thus, the study is based on non-selective population data.

The researchers excluded from the study women who delivered only once, multiple pregnancies, unknown gestational age, fetuses with major congenital malformations or chromosomal abnormalities, and all perinatal mortality cases (intra-uterine fetal death, intra-partum death and post-partum death).

3. Operational Definition of Variables

Short IPI was defined as less than 6 months, intermediate IPI (between 6 to 60 months), and long IPI was defined as an IPI of (more than 60 months).

The variables obtained for the analysis included the following maternal factors: maternal age, parity, hypertensive disorders in pregnancy, diabetes in pregnancy, and maternal obesity. Perinatal factors obtained included: gestational age and preterm delivery, and birthweight.

The outcome variables included the following major pediatric metabolic diseases: diabetes mellitus, obesity, sex hormone disease, hypoglycemia and hyperlipidemia. All diagnoses are classified by the international classification of disease (ICD-9, appendix A).

4. Study Instruments

In this population-based retrospective cohort study, data were collected from two computerized databases that were cross-linked and merged. The first, was the perinatal database of the Obstetrics and Gynecology department in SUMC, including information documented by obstetricians following each delivery. Experienced medical secretaries routinely review the information before entering it into the database to ensure its maximal completeness and accuracy. Coding was performed after assessing medical prenatal care records as well as routine hospital documents.

The second, was the SUMC general hospitalization records for children up to the age of 18 years, which includes demographic data and medical diagnoses obtained upon admission and during hospitalization.

5. Data Analysis

Univariable analysis was performed to compare background characteristics, and endocrine and metabolic morbidity, between the three study groups.

The univariable analysis included Pearson Chi-square tests for categorical variables and ANOVA for continuous variables with normal distribution. The comparison was performed across all levels of exposure: short, intermediate and long IPI. Cumulative incidence rates of endocrine and metabolic related hospitalizations of the offspring were compared using Kaplan-Meier survival curve, using the log-rank test to determine significant differences. Two dummy variables were defined as short and long IPI groups. Those variables were created to compare the short and long IPI groups to the intermediate reference group.

Cox proportional survival hazards model was conducted to compare endo-metabolic associated hospitalizations risk among offspring born following a short or a long IPI. The model was adjusted for potential confounders based on the univariable analysis, and on clinical importance of the variables. The confounders included in the regression model were maternal factors (age, diabetes mellitus, obesity and hypertensive disorders), as well as obstetrical factors (birthweight and gestational age upon delivery). All analyses were performed using SPSS (version 23) or STATA (version 12) software. All analyses were 2-sided; and

a p value of less than 0.05 was considered significant.

6. Research Ethics

The institutional review board, in accordance with the Helsinki declaration, approved the study.

RESULTS

1. Sample Characteristics

The inclusion criteria were met by 161,791 deliveries during the study period. Of those 22,851 (14.1%) occurred in women with short IPIs, 127,144 (78.6%) in women with intermediate IPIs, and 11,796 (7.3%) in women with long IPIs. Table 1a summarizes maternal characteristic for the different IPI categories. Mean maternal age upon delivery was different among the IPI groups. Mothers in the long IPI group were also more likely to be diagnosed with hypertensive disorders of pregnancy and diabetes (pre-gestational and gestational) with a high incidence of 10.2% in the long IPI group as compared to the intermediate (4.9%) and short (2.9%) IPI groups.

Pregnancy outcomes are shown in Table 1b. Mean birthweight was smaller in the short IPI group and low Apgar score rates were higher in that group. The short and long IPI groups were both characterized by higher rates of preterm delivery and low birth-weight, as compared with the intermediate IPI group.

Table 1a. Maternal characteristics (continuous data) by interpregnancy interval (IPI)

Characteristics	Long IPI (>60 months)		Intermediate IPI (6-60 months)		Short IPI (<6 months)	
	Mean	SD	Mean	SD	Mean	SD
Maternal age (year)	34.50	4.28	29.2	5.33	26.14	5.07

Table 1b. Maternal characteristics (categorical data) by interpregnancy interval (IPI)

Characteristics	Long IPI (>60 months)		Intermediate IPI (6-60 months)		Short IPI (<6 months)	
	n	%	n	%	n	%
Parity						
2 to 4	9,241	78.3	80,938	63.7	15,829	69.3
5+	2,555	21.7	46,208	36.3	7,022	30.7
Hypertensive disorder*	810	6.9	5,172	4.1	615	2.7
Diabetes in Pregnancy**	1,202	10.2	6,251	4.9	673	2.9
Obesity (BMI≥30 Kg/m²)	167	1.4	1340	1.1	189	0.8

* Including pre-gestational, gestational hypertension, and preeclampsia.

** Including pre-gestational and gestational diabetes mellitus.

2. The result of bivariate analysis

Long-term endocrine and metabolic hospitalization rates of offspring according to maternal IPI duration, are presented in Table 2a. During the 18-year follow-up period, 690 children were hospitalized with endocrine and metabolic morbidity. Children born following long IPIs exhibited higher rates of endo-metabolic related hospitalizations, as compared with the intermediate and short IPI groups (0.8% vs. 0.5% vs. 0.4% respectively). Specifically, diabetes mellitus and obesity were more common in offspring born following long IPI.

Table 2a. Pregnancy outcomes (continous data) by interpregnancy interval (IPI)

Outcomes	Short IPI (<6 months)		Intermediate IPI (6-60 months)		Long IPI (>60 months)		p
	Mean	SD	Mean	SD	Mean	SD	
Birth weight (gram)	3,171.2	487.4	3,258.1	497.5	3,235.6	516.2	<0.001
Gestational age (weeks)	39.06	1.97	39.18	1.92	38.85	2.02	<0.001

Table 2b. Pregnancy outcomes (categorical data) by interpregnancy interval (IPI)

Characteristics	Short IPI (<6 months)		Intermediate IPI (6-60 months)		Long IPI (>60 months)		p
	n	%	n	%	n	%	
Gender							
Male	1,575	50.7	64,656	50.9	5,925	50.1	0.315
Female	1,276	49.3	62,490	49.1	5,881	49.9	
Preterm delivery	1,799	7.9	7,498	5.9	909	7.7	<0.001
Low birth weight (<2500 g)	1,569	6.9	6,637	5.2	782	6.6	<0.001
Apgar score <7 at 1 min	1,272	5.6	6,374	5	550	4.7	<0.001
Apgar score <7 at 5 min	786	3.4	3,088	2.4	162	1.4	<0.001

Table 3. Selected long-term endocrine and metabolic morbidity of offspring born stratified by different interpregnancy interval (IPI) lengths.

Offspring Long-Term Morbidity	Short IPI (<6 months)		Intermediate IPI (6-60 months)		Long IPI (>60 months)		p
	n	%	n	%	n	%	
Thyroid disease	7	0.03	59	0.1	6	0.1	0.694
Diabetes mellitus	10	0.1	110	0.1	16	0.1	0.048
Hypoglycemia	23	0.1	138	0.1	21	0.3	0.195
Hyperlipidemia	0	0	1	0.0008	0	0	0.875
Obesity	30	0.2	180	0.2	38	0.3	<0.001
Parathyroid disease	3	0.0001	21	0.0002	3	0.0003	0.805
Adrenal disease	4	0.0002	20	0.02	4	0.0003	0.943
Sex hormone disease	0	0	11	0.0001	4	0.0003	0.013
Total endo-metabolic related hospitalization	75	0.4	528	0.5	87	0.8	<0.001

3. The result of multivariate analysis

The Kaplan-Meier survival curve (Figure 1) demonstrated a significantly higher cumulative incidence of long-term endocrine and metabolic morbidity in the long IPI group (log rank p<0.001). Table 4 presents the Cox proportional hazards model for the association between IPI and offspring long term endocrine and metabolic morbidity. The model controlled for maternal age, diabetes mellitus, hypertensive disorders, and obesity, as well as preterm delivery and birthweight. The model confirmed that infants born following long IPIs were at a significant and independent risk for long-term endocrine and metabolic related hospitalizations during childhood (adjusted HR=1.34, 95%CI=1.06 to 1.70; p=0.015).
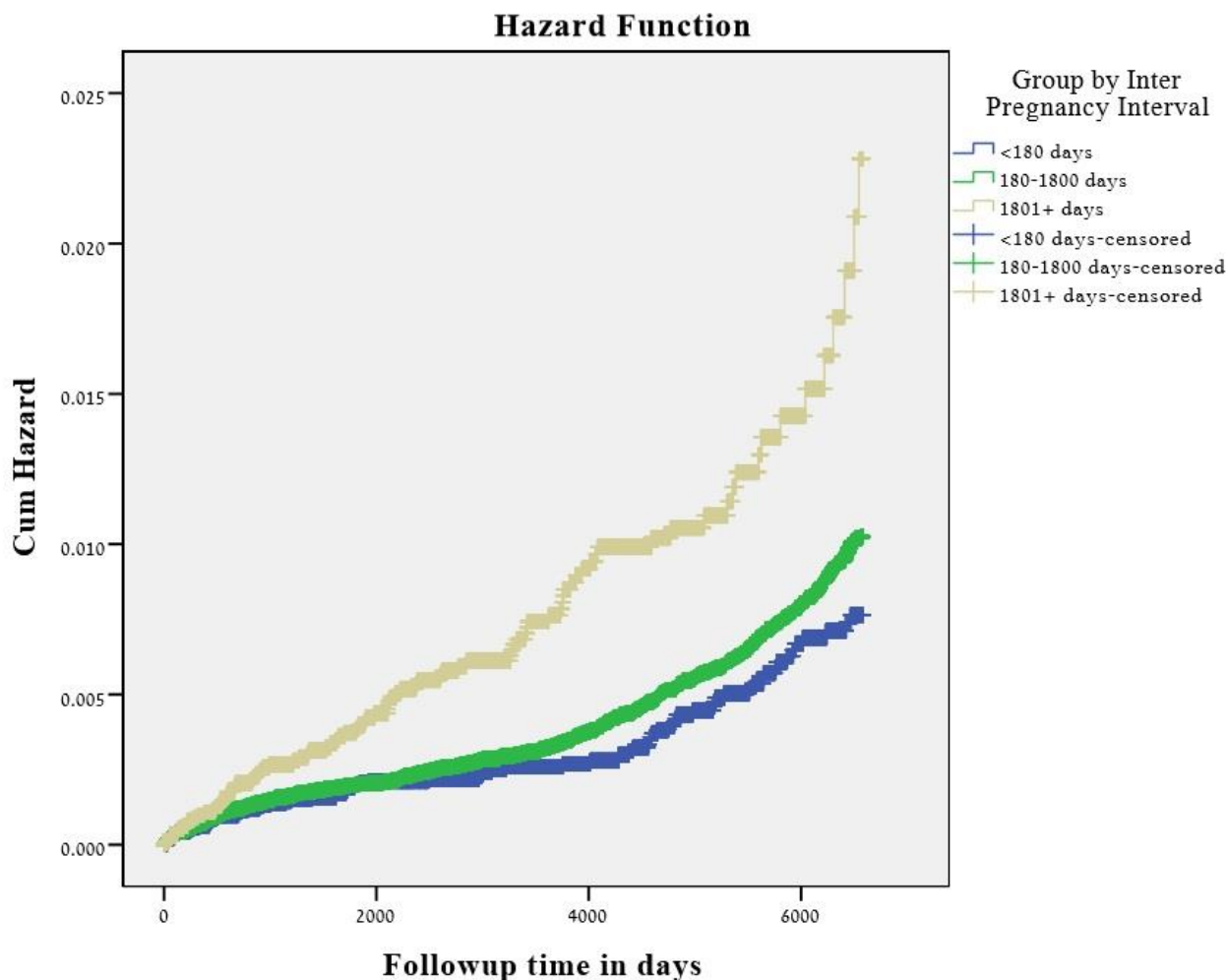
Figure 1. Kaplan-Meier survival curve for the cumulative incidence of endocrine and metabolic hospitalizations over time, from birth up to 18 years of age, according to inter pregnancy interval (log-rank p<0.001).

Table 4. Multivariable analysis for the association between interpregnancy interval (IPI) and offspring long term endocrine and metabolic morbidity.

Independent Variables	adjusted Hazard Ratio	95% CI		p
		Lower limit	Upper limit	
Intermediate IPI				
Long IPI (>60 months)	1.34	1.06	1.70	0.015
Short IPI (<6 months)	1.01	0.79	1.31	0.88
Maternal age (years)	0.96	0.94	0.97	<0.001
Preterm delivery (<37 weeks)	1.28	0.96	1.72	0.1
Birthweight (grams)	0.99	0.99	1.00	0.12
Hypertensive disorders of pregnancy	1.21	0.89	1.66	0.23
Diabetes mellitus (gestational and pre-gestational)	1.67	1.29	2.16	<0.001
Obesity (BMI≥30 Kg/m^2)	2.62	1.72	3.98	<0.001

DISCUSSION

The researchers found that long IPI is strongly associated with an increased incidence of long-term endocrine and metabolic morbidity of the offspring. Specifically, a significantly increased risk for diabetes mellitus and obesity in offspring born following long IPIs was demonstrated, as compared with the intermediate and short IPI groups. This original observation raises the question of whether long IPI represents an independent risk factor or whether this association can be explained by maternal and obstetrical confounding factors. Due to the large size of the cohort, the researchers were able to design a multiple logistic regression analysis controlling for many potential confounding factors. Factors controlled for in the model included maternal factors like age, diabetes mellitus, obesity and hypertensive disorders, and obstetrical factors such as birthweight and preterm delivery.

Current published literature focuses mainly on the significant effect of a short IPI and adverse perinatal outcome. For instance, short IPI had been associated with pre-term delivery, neonatal and fetal death, LBW, and SGA (Conde-Agudelo et al., 2006; Mahande and Obure, 2016; Cecatti et al., 2008; Mignini et al., 2016). Long IPI, however, has been less investigated, yet some important associations have been suggested, including the risk for preterm delivery, LBW, SGA, fetal death, and increased odds of pre-eclampsia (Cecatti et al., 2008; Class et al., 2017; Mahande and Obure, 2016; Cecatti et al., 2008; Mignini et al., 2016; Kaul et al., 2019). As for the association between IPI and long-term health of the offspring, data is scarce. Li et al. (2018) suggested that long IPI is a risk factor for higher diastolic BP in offspring, which can potentially be explained by the confounding effect of advanced maternal age (Li et al., 2018).

The prevailing view today is that endocrine and metabolic disease is not only determined by one's genes, but also by the prenatal (i.e. intra-uterine) environment. This is in line with the currently widely accepted Barker hypothesis. Barker claimed that the fetus can be expected to make physiological adaptations in response to changes in its environment, in order to prepare itself for postnatal life (De Boo and Harding, 2006). For example, Barker's 'thrifty phenotype' hypothesis suggested that adult insulin resistance and type 2 diabetes could result from the persistence of a fetal glucose conserving adaptation in response to intrauterine hypoglycemia (De Boo and Harding, 2006). This is consistent with a recent study suggesting an association between in utero exposure to gestational diabetes (GDM) and long-term infant endocrine and metabolic morbidity, e.g. higher blood pressure and a predisposition for obesity, impaired glucose tolerance, diabetes, and metabolic syndrome (Abokaf et al., 2018).

Long IPI is strongly linked with factors that could influence the prenatal environment. For instance, maternal age and weight, as well as nutritional status. The association between IPI and endo-metabolic morbidity has not been previously studied. Therefore, the possibility that long IPI is independently linked with offspring endocrine and metabolic morbidity during childhood is of significant public health interest, as birth spacing is recognized as a modifiable risk factor (Regan et al., 2019).

The major strength of the present study is the large sample upon which it is based. This allowed to control for several important confounding factors. Although the retrospective nature of this study is an

obvious limitation, the data was collected prospectively and recorded in real-time. Moreover, this study is based on non-selective population data. The authors used pre-tested, standardized data collection forms, completed by trained data collectors, and a methodology based on a previous WHO global survey (Shah, 2008). Furthermore, since the medical center is the only one in the region, most children born in the hospital are likely to return to our center for medical treatment if warranted. The authors therefore believe that as a regional hospital our study population included a relatively unbiased participation of mothers from all socioeconomic backgrounds.. It is also apparent that a randomized controlled study regarding the effects of IPI will not be possible, as mothers are not likely to agree to base their family planning decisions solely on a random study allocation.

This study has several limitations. First, it is based on a large hospital-based database that does not include outpatient visits at non-hospital affiliated clinics. Therefore, cases of endocrine and metabolic disease managed solely in an outpatient setting were not accounted for. Furthermore, although the population is relatively non-mobile, it is clear that some patients may have moved to other regions and therefore missed, although these two limitations are true for all three study groups.

Since this is a population-based analysis, this study can provide evidence only of an association rather than causation. Several potentially important factors were not available, such as childhood exposures, breast feeding, maternal weight or body mass index and socio-economic status. These factors have previously been shown to affect or protect the risk of endocrine and metabolic diseases (Boney et al., 2005; Kaul et al., 2019). For instance, lack of breast-feeding in the first 5 months of life was associated with higher likelihood of being overweight in childhood (Boney et al., 2005).

In conclusion, our observation, that long IPI is significantly associated with an increase in long-term endocrine and metabolic morbidity of the offspring, adds an important perspective to be considered during family planning. It seems that women can now be advised that prolonging the interval between births may increase endocrine and metabolic risk in their child. Further study is needed to assess whether this association can be attenuated 15 by interventions such as healthy lifestyle, weight maintenance, or physical activity. It remains to be seen whether counseling to optimize birth spacing can significantly reduce endocrine and metabolic mortality, and improve other immediate and long term pregnancy outcomes (Class et al., 2017; Li et al., 2018; Conde-Agudelo et al., 2006).

Better understanding of this association may therefore lead to practical public health recommendations and interventions, within the realm of family planning and disease prevention, in both the developed and developing world.

AUTHOR CONTRIBUTION

Seidman L. has participated in all phases of this study including planning, literature search, data interpretation, and has written the first draft of the manuscript. Wainstock T. is a specialist in performing all aspects of the statistical analysis needed for this study. She has participated in all phases of this study and has performed most of the analyses presented in this paper. Sheiner E. has initiated the study and supervised actively throughout its conduct. Specifically, he was involved in the data interpretation, statistical analysis, and has

revised the manuscript. Pariente G. has participated in all phases of this study including literature search and research planning, data collection and review, and took part in the data interpretation. Sergienko R. managed data collection, built the database and planned the statistical analysis. Walfisch A. has initiated and participated in all phases of this study including study planning, literature search, data collection and review, interpretation of the results, and has supervised and extensively revised the manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest in this study.

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