Implications of Nonalcoholic Fatty Liver Disease on Pregnancy and Maternal and Child Outcomes

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Abstract: With an estimated 10% prevalence of nonalcoholic fatty liver disease (NAFLD) among women of childbearing age, it is important to understand the implications of this disease on pregnancy. This article explores the relationship between NAFLD and gestational diabetes mellitus, the implications of maternal NAFLD on both the pregnancy and the infant, and the effects of breastfeeding on maternal and offspring health. Prospective studies and sensitive diagnostic techniques for the evaluation of NAFLD during pregnancy are limited; however, emerging evidence suggests that appropriate counseling and monitoring of patients with, or at risk of developing, NAFLD during pregnancy may have significant benefits on maternal and child health.

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in the Western world, with an estimated prevalence of 20% to 30% in the adult population, 6.67% to 29.85% of whom progress to more advanced nonalcoholic steatohepatitis (NASH).[1,2] NAFLD is also the leading indication for liver transplantation among women.[3,4] The prevalence of NAFLD varies by age, sex, ethnicity, modality of diagnosis, and prevalence of obesity in the population.[5] The disorder is closely tied to the metabolic syndrome of central adiposity, diabetes mellitus (DM), hypertension, and hyperlipidemia, with DM independently conferring a 2-fold increased risk of NAFLD.[6] However, even among individuals with these risk factors, NAFLD is not ubiquitous, suggesting significant contributions from other genetic and environmental factors as well.[7] NAFLD progresses as a result of a complex sequence of events involving excess lipotoxicity in the setting of surplus free fatty acids, peripheral adiposity, and hepatic insulin resistance, which, in turn, promotes proinflammatory cytokines such as tumor necrosis factor–alpha and interleukin-6, and eventually activates stellate cells and scar tissue deposition in the liver.[8]

The prevalence of NAFLD among women of childbearing age (20-40 years old) is estimated to be 10%.[9] Thus, the effects of NAFLD on pregnancy-related outcomes and maternal and child health are of great interest. Physiologic and pathologic estrogen

fluctuations and rapid weight change during pregnancy may play important roles in NAFLD development in both mother and infant. In addition, recent data show a vulnerability to insulin resistance patterns during pregnancy, particularly as seen in gestational diabetes mellitus (GDM), both as the preceding and subsequent diagnosis to NAFLD.[10-12] The deleterious effects of maternal hyperglycemia and weight gain are well-established on pregnancy complications and infant health,[13,14] but data regarding the specific effect of NAFLD in this setting are only beginning to emerge. This article summarizes the current knowledge of the implications of NAFLD on pregnancy as well as on maternal and child health.

Nonalcoholic Fatty Liver Disease and Gestational Diabetes Mellitus

GDM is the most common metabolic disorder during pregnancy. Given the established link between DM and NAFLD, emerging data have explored the relationship between GDM and NAFLD. To date, the association between NAFLD and GDM appears to be bidirectional (Table). For example, a study by De Souza and colleagues[15] demonstrated that NAFLD found on a first-trimester ultrasound had a higher risk of GDM and dysglycemia developing in midpregnancy, independent of body mass index (BMI). This finding was replicated by Lee and colleagues[16] in a prospective, multicenter cohort study in which singleton pregnant Korean women were assessed at 10 to 14 weeks gestation. Low adiponectin and high selenoprotein-P levels were found to be related in stepwise fashion with sonographic and biochemical severity of NAFLD, and were independent predictors of GDM later in pregnancy. These proinflammatory cytokines may become useful future biomarkers in predicting both the severity of NAFLD and the risk of GDM development independent of coexisting metabolic factors; however, mechanistic studies are needed.

Prior GDM (pGDM) has also been associated with postpartum development of NAFLD. The multicenter, community-based, longitudinal CARDIA (Coronary Artery Risk Development in Young Adults) cohort study[17] established a diagnosis of NAFLD at 25-year follow-up using computed tomography quantification of liver attenuation of 40 or less Hounsfield units (corresponding with moderate to severe hepatic steatosis above 30%). When evaluating a self-report of pGDM,[10] which had previously been validated,[18] there was a crude NAFLD risk of 14% in patients with pGDM vs 5.8% without pGDM (odds ratio [OR], 2.56; 95% CI, 1.44-4.55). In the final multivariable model, baseline triglyceride levels, pGDM, and baseline Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were independently associated with NAFLD to year 25.[10] Limitations of this study include the high liver attenuation cutoff with reduced sensitivity for detecting mild steatosis. Furthermore, with no baseline NAFLD screening, the interpretation of the exact temporal relationship between GDM and NAFLD was hard to determine. The CARDIA study showed a 4-fold increased risk of developing DM after pGDM; however, it may have been underpowered to demonstrate an independent association of pGDM alone with NAFLD, as the relationship between pGDM and NAFLD was significantly attenuated when progression to DM was included in the multivariable analysis.[10]

Controlling for postpartum BMI, Forbes and colleagues[11] compared sonographic results under 10 years after the index pregnancy of women with and without a documented abnormal antepartum 2-hour, 75-g oral glucose tolerance test or who met World Health Organization criteria for GDM[19] who had not developed DM. NAFLD was identified in 38% of patients with pGDM (95% CI, 28%-47%) vs 17% without (95% CI, 10%-24%; P=.001). When adjusting for BMI, the OR for NAFLD with pGDM remained doubled. This association was demonstrated, although to a lesser degree, by Foghsgaard and colleagues,[12] with NAFLD present in 24% of women with pGDM without DM. Similar to other research, aspartate aminotransferase and alanine aminotransferase levels were unreliable predictors of NAFLD.[5] The presence of NAFLD was associated with a higher BMI, waist circumference, insulin resistance, and delayed suppression of glucagon on dynamic glucose testing.[12]

Although Foghsgaard and colleagues[12] did not replicate the known association of NAFLD and pre-DM,[20] higher levels of C-peptide on dynamic glucose testing in the combined NAFLD and pGDM group compared with pGDM alone suggest early pancreatic dysfunction among the former cohort. Mehmood and colleagues[21] provided further evidence for NAFLD stimulating insulin-resistant disorders, such as pre-DM and type 2 DM. The authors found that as sonographic-graded severity of liver fat increased, there was a progressive worsening of insulin sensitivity and beta-cell function, coupled with rising fasting and 2-hour glucose (P<.001) on 75-g oral glucose tolerance test. Moderate liver fat was an independent predictor of current pre-DM or DM (OR, 3.66; 95% CI, 1.1-12.5). The mechanism by which NAFLD causes impaired glucose tolerance is not well-defined, although it is likely due to a shared metabolic pathway.[16] A proinflammatory adipokine- and hepatokine-mediated response may explain the association of NAFLD with GDM and/or DM in the absence of other metabolic risk factors, and, when present, their independent association after multivariate regression.

Table. Studies Evaluating the Relationship Between GDM and NAFLD

Predictor and Outcome Factor	Number of Subjects, n	Timing of Association	NAFLD Criteria	Diagnostic Criteria of GDM (Glucose mmol/L)	Association OR/RR (95% CI)	Multivariable Adjusted Association aOR/aRR (95% CI)	Other Significant NAFLD Factors aOR/aRR (95% CI)
Forbes et al[11]							
Predictor: Prior GDM Outcome factor: NAFLD	Prior GDM, 110 Control, 113	1-10 years postpartum	US-graded steatosis	75 g OGTT: FPG ≥7; 2 hr ≥7.8	N/A	aOR, 2.77[a] (1.43-5.37)	HOMA insulin sensitivity/1 SD: aOR, 0.08 (0.04-0.19) ALT/1 SD (13 U/L): aOR, 2.85 (1.63-4.98)
Ajmera et al[10]							
Predictor: Prior GDM Outcome factor: NAFLD	Prior GDM, 124 Control, 991	Study enrollment to year 25	CT LA ≤40 HU	Self-report	OR, 2.56 (1.44-4.55)	aOR, 2.29 (1.23-4.27)	Baseline HOMA-IR: aOR, 1.56 (1.2-2.04) Baseline triglycerides: aOR, 1.05 (1.01-1.11)
De Souza et al[15]							
Predictor: NAFLD at 11-14 weeks Outcome factor: IFG/ IGT/ GDM at 24-48 weeks	Total, 476	Peripartum	US-graded steatosis	75 g OGTT: FPG ≥5.3; 1 hr ≥10.6; 2 hr ≥8.9	OR, 2.5 (1.3-4.8)	aOR, 2.2 (1.1-4.3)	N/A
Hagström et al[22]							
Predictor: NAFLD Outcome factor: GDM	NAFLD, 110 Control, 952,397	Peripartum	ICD-9, ICD-10	ICD-9, ICD-10	RR, 6.77 (3.31-13.87)	aRR, 2.78 (1.25-6.15)	Preeclampsia: aRR, 1.95 (1.03-3.70) Caesarean section: aRR, 1.52 (1.19-1.94) Low birth weight: aRR, 2.40 (1.21-4.78) Delivery <32 weeks: aRR, 6.92 (2.96-16.14)
Foghsgaard et al[12]							
Predictor: Prior GDM Outcome factor: NAFLD	Prior GDM, 100 Control, 11	Median 4.5-4.8 years postpartum	US	75 g OGTT: 2 hr ≥9	N/A	N/A	IR: aOR, 0.44 (0.23-0.75) Waist circumference: aOR, 1.07 (1.02-1.12)

(Table continued on next page)

Table. *(Continued)* Studies Evaluating the Relationship Between GDM and NAFLD

Predictor and Outcome Factor	Number of Subjects, n	Timing of Association	NAFLD Criteria	Diagnostic Criteria of GDM (Glucose mmol/L)	Association OR/RR (95% CI)	Multivariable Adjusted Association aOR/aRR (95% CI)	Other Significant NAFLD Factors aOR/aRR (95% CI)
Mehmood et al[21]							
Predictor: GDM Outcome factor: NAFLD	GDM, 97 Gestational IGT, 40[b] Control, 120	Mean 4.8 years postpartum	US-graded steatosis	100 g OGTT: FPG ≥5.8; 1 hr ≥10.6; 2 hr ≥9.2; 3 hr ≥8.1	OR, 3.66 (1.1-12.5)	N/A	N/A
Mousa et al[23]							
Predictor: NAFLD Outcome factor: GDM	NAFLD, 200 Control, 200	Peripartum	US	75 g OGTT: FPG ≥7; 2 hr ≥11.1	33% with NAFLD vs 10% without	N/A	N/A
Lee et al[16]							
Predictor: NAFLD at 10-14 weeks Outcome factor: GDM at 24-48 weeks	NAFLD, 112 GDM, 36 Total, 608	Peripartum	US-graded steatosis, fatty liver index, hepatic steatosis index	50 g GCT: 1 hr ≥7.8 100 g OGTT ≥2: FPG ≥5.3; 1 hr ≥10; 2 hr ≥8.6; 3 hr ≥7.8	OR, 6.45 (3.26-12.97)	N/A	N/A

[a]Univariate adjustment for body mass index.

[b]Gestational IGT defined by only 1 OGTT value above threshold.

ALT, alanine aminotransaminase; aOR, adjusted odds ratio; aRR, adjusted relative risk; CT LA, computed tomography quantification of liver attenuation; FPG, fasting plasma glucose; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HOMA, Homeostatic Model Assessment; hr, hour; HU, Hounsfield units; ICD, International Classification of Disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; N/A, not available; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk; SD, standard deviation; US, ultrasound.

Maternal Nonalcoholic Fatty Liver Disease Outcomes in Pregnancy

Several studies have suggested negative pregnancy outcomes with comorbid NAFLD. From the Swedish Medical Birth Register dating from 1992 to 2001, 110 births with maternal NAFLD were retrospectively identified, although likely underdiagnosed compared to epidemiologic data.[22] Baseline demographics showed higher BMI and DM rates among patients with NAFLD. Compared to women without polycystic ovary syndrome (an independent risk factor for NAFLD) or NAFLD, women with NAFLD had a higher risk of GDM (adjusted relative risk [aRR], 2.78; 95% CI, 1.25-6.15), preeclampsia (aRR, 1.95; 95% CI, 1.03-3.70), Caesarean section (aRR, 1.52; 95% CI, 1.19-1.94), low birth weight (aRR, 2.40; 95% CI, 1.21-4.78), and very preterm (<32 weeks) delivery (aRR, 6.92; 95% CI, 2.96-16.14). There were no differences in frequency of Apgar score (<7 at 5 minutes), congenital malformations, or small for gestational age births. Interestingly, when dividing the NAFLD maternal cohort by BMI less than 30 or BMI 30 or greater, NAFLD independently conferred an increased risk of preeclampsia and GDM in the lower-BMI cohort only.

Obesity is a recognized independent risk factor for both GDM and preeclampsia,[13,14] suggesting that the

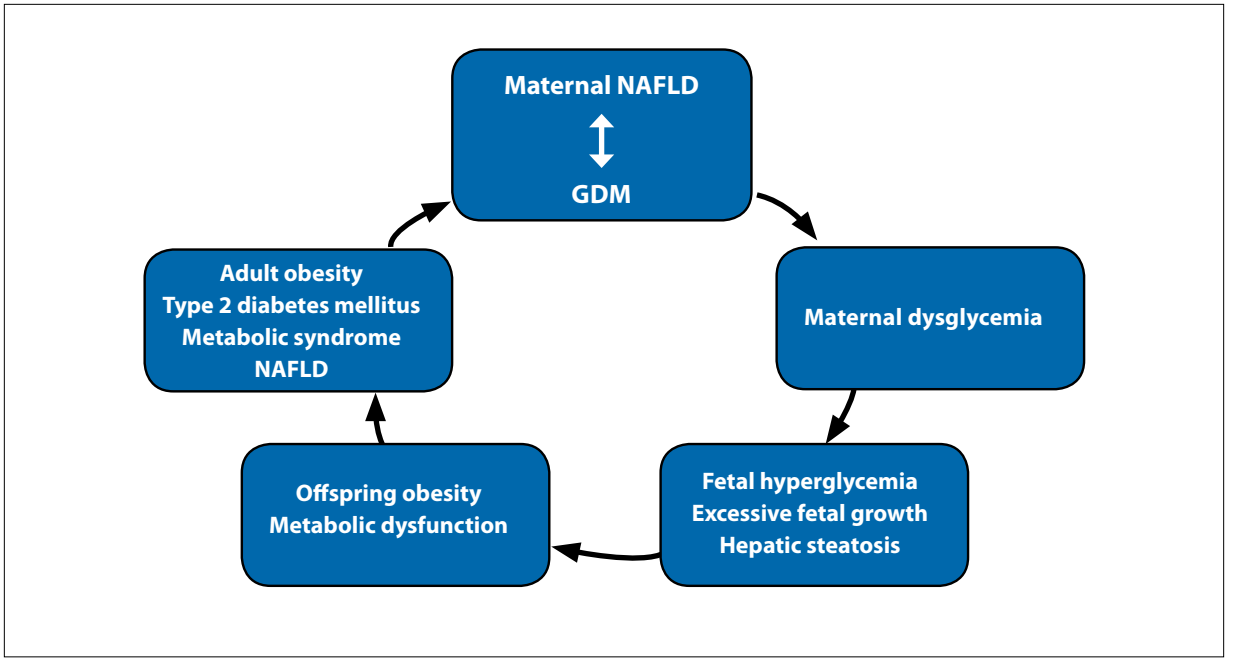

Figure. Proposed transgenerational effects of maternal NAFLD and GDM.
GDM, gestational diabetes mellitus; NAFLD, nonalcoholic fatty liver disease.

association seen between obese patients with NAFLD and these outcomes may be driven by body composition. Excluding women who were multiparous, diabetic prior to study initiation, diagnosed with polycystic ovary syndrome, and who smoke or drink alcohol, Mousa and colleagues[23] compared a population of 200 Egyptian women meeting sonographic criteria for NAFLD in their first trimester to matched controls. The authors found higher frequencies of concomitant preeclampsia (25% vs 14%) and GDM (33% vs 10%) among women with NAFLD, as well as higher levels of hypertension, fasting glucose, aspartate aminotransferase (but not alanine aminotransferase), total cholesterol, triglycerides, and uric acid. Both groups had a normal baseline mean BMI (NAFLD, 24.5; non-NAFLD, 24.4), making extrapolation to obese NAFLD patients difficult. These findings need to be further validated with larger prospective studies of NAFLD in pregnancy.

Effects of Maternal Nonalcoholic Fatty Liver Disease on Infants

Some studies have suggested that metabolic syndrome originates from insults in utero, including overnutrition and anoxia.[13,24] The expanded Pedersen hypothesis proposes that elevated maternal glucose during pregnancy results in fetal hyperglycemia leading to fetal hyperinsulinemia and excessive fetal growth by means of reprogrammed insulin sensitivity, shifts in lipid metabolism, and increased placental transfer of free fatty acids.[25-27] In addition to the immediate postnatal complications (eg, shoulder dystocia, birth injury, hypoglycemia, respiratory distress), prenatal exposure to hyperglycemia and DM can form the foundation for a lifelong predisposition to metabolic dysfunction evidenced by obesity and increased adiposity in all stages of life.[28-31] Furthermore, maternal obesity promotes preferential differentiation of mesenchymal umbilical cord cells into adipocytes rather than myocytes in newborn babies, correlating with an increase in neonatal adiposity within 72 hours of birth.[32] This evidence suggests that the intrauterine environment may respond to metabolic insults in a way that imprints a persistent inclination toward metabolic dysfunction, underlying the proposed vicious cycle whereby metabolic conditions may be passed from generation to generation (Figure).

Beyond offspring obesity and DM, maternal metabolic derangements induce hepatic changes in the infant that can increase the risk of future NAFLD development. Stillborn babies born to mothers with DM, including GDM and pre-DM, were found to have increased prevalence and severity of histopathologic hepatic steatosis independent of maternal obesity.[33] Maternal insulin resistance, independent of hyperglycemia or obesity, leads to greater glucose intolerance, hyperinsulinemia, fasting hyperglycemia, lipid accumulation in the liver,

and plasma free fatty acids in mice offspring.[24,34] Infants born to obese mothers with GDM had a 68% increase in intrahepatocellular fat.[35]

Looking past neonatal outcomes, a large British prospective cohort study found that maternal prepregnancy DM or glycosuria was associated with a 6-fold increase in the odds of offspring NAFLD (mean age, 17.8 years) by ultrasound criteria and a higher shear velocity, even after adjusting for maternal prepregnancy BMI.[36] However, the association of maternal prepregnancy BMI and NAFLD in offspring was attenuated to the null when adjusted to the offspring adiposity, suggesting that familial characteristics (genetic or behavioral) related to adiposity may outweigh direct uterine effect. Although estimates of genetic heritability of NAFLD are broad, isolated genetic variants such as patatin-like phospholipase domain-containing protein 3 (PNPLA3) are shown to be associated with increased hepatic fat content independent of BMI, DM status, alcohol use, or ancestry.[37,38]

Sex dimorphisms in offspring may confer different risks for NAFLD development. For example, the frequency of adolescent Australian females with NAFLD increased incrementally with maternal prepregnancy BMI category, from underweight or normal (18.2%), to overweight (23.1%), to obese (41.2%).[39] In female offspring, maternal BMI category was associated with increased adolescent waist circumference, serum leptin, and glucose, whereas this maternal factor correlated with leptin alone in male offspring. The effect of maternal prepregnancy BMI category was, thus, less profound in males (9.3% vs 14.3% vs 26.7%), and NAFLD in males was more closely related to the degree of adolescent obesity. Beyond genetic inheritance, peripartum maternal NAFLD may play a role in the development of NAFLD in the next generation, possibly through association with GDM and other metabolic risk factors; however, further studies are needed to isolate these effects.

Effects of Breastfeeding on Maternal Health

Maternal benefits of breastfeeding include postpregnancy weight loss, lowered glucose and triglycerides, and improved insulin sensitivity.[40,41] Ajmera and colleagues[42] recently published the first dedicated evaluation of breastfeeding on NAFLD development at year 25 utilizing the CARDIA cohort.[17] Crude NAFLD rates inversely correlated with self-reported lactation duration at 8.3% for 0 to 1 month, 7.7% for 1 to 6 months, and 4.2% for more than 6 months. However, the combination of any breastfeeding compared to none did not have a statistically significant protective association against NAFLD, suggesting a threshold effect of more than 6 months. Baseline data found that women with longer lactation duration had lower BMI, HOMA-IR, triglycerides, and waist circumference and increased physical activity, whereas GDM status did not differ. Mean changes in BMI and waist circumference were inversely related to lactation duration. Adjusted linear regression suggested that changes in BMI and waist circumference account for 20% and 23% of NAFLD hazard, respectively, and, thus, lactation duration represented an independent risk factor. An observational cohort study of pGDM patients at a mean of 4.8 years postpartum likewise showed that the sonographic degree of liver fat was inversely related to duration of breastfeeding.[21]

Socioeconomic and cultural factors may influence preference for breastfeeding, yielding further diversity in related outcomes. Lower family socioeconomic status at the time of birth increased the odds of male offspring adolescent NAFLD development (OR, 9.07; 95% CI, 1.54-53.29), which may be explained in part due to males being half as likely to have been breastfed for more than 6 months in this study.[39] Interestingly, the inverse association of lactation duration and NAFLD did not reach statistical significance when evaluating black women in the CARDIA cohort.[42] This finding may be related to genetic influence, including from the PNPLA3 genotype, and/or hypoattenuated effects related to lower socioeconomic status, education, and physical activity levels and poorer diet quality. To date, there are limited data recognizing women of Hispanic origin with regard to NAFLD-specific pregnancy outcomes, and the CARDIA database did not distinguish this population.

Effects of Breastfeeding and Early Nutrition on Offspring Health

Early environmental experiences, including the supply of nutrients during intrauterine and early extrauterine life, are suggested to affect the development of chronic diseases. Beyond nutritional support, breastfeeding benefits include potential reductions in the rates of childhood obesity, allergies, infection, and DM.[43] Duration of breastfeeding and content of diet early in infant life may have profound effects on the risk of NAFLD. Nobili and colleagues[44] reported the first observational study to demonstrate that breastfeeding was associated with a lower risk of biopsy-proven NASH in 3- to 18-year-old children, with an OR of 0.04 (95% CI, 0.01-0.10) after correction for age, waist circumference, gestational age, and neonatal weight. Furthermore, odds of pediatric NASH (OR, 0.7; 95% CI, 0.001-0.87) and fibrosis (OR, 0.86; 95% CI, 0.75-0.98) decreased per month of breastfeeding.[44] A more favorable metabolic profile was demonstrated in an Australian cohort of pediatric patients who were breastfed for at least 6 months, with earlier

use of supplements associated with higher prevalence of NAFLD (17.7% vs 11.2%) and more severe steatosis.[45] However, crude odds of NAFLD were not significant when adolescent obesity was adjusted for. Animal models suggest that a high-fat diet in early infancy, via lactation or postweaning, may exaggerate NAFLD risk and severity, independent of maternal obesity.[46-48] Liver biopsies in mice suggest that this finding may be due to reduced hepatic mitochondrial electron transport chain enzyme complex activity, a driver of insulin resistance, and/or upregulation of genes related to oxidative stress and lipogenesis, including endothelial nitric oxide synthase, inducible nitric oxide synthase, glutathione S-transferase mu 6, and lipocalin 2.[48] It is not yet well-established whether these same mechanisms drive the correlation of excess caloric intake with NAFLD in human adult populations.

Conclusion

Given the multiple complex genetic and environmental factors involved with NAFLD, there is still much to be learned about the specific intra- and extrauterine contributing mechanisms of disease. The causal relationship between hepatic fat content, insulin resistance, and dyslipidemia remains poorly defined. The overlapping features of metabolic syndrome make distinguishing each metabolic risk factor's contribution to NAFLD during pregnancy difficult with retrospective studies. Further prospective studies are necessary to elucidate the association between NAFLD and pregnancy-specific features such as GDM, as well as the true impact of NAFLD on pregnancy outcomes. The effects of maternal metabolic syndrome, insulin resistance, NAFLD, and both intra- and extrauterine dietary content appear to play a role in the development of NAFLD in the infant, although mechanisms need to be further evaluated. Controlling antepartum hyperglycemia, preventing GDM, and avoiding excess weight gain during pregnancy, as well as encouraging lactation for more than 6 months, may help reduce the burden of NAFLD among mothers and their children.

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