Pregnancy and Metabolic-Associated Fatty Liver Disease

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KEYWORDS

• Children • Metabolic-associated fatty liver disease • Nonalcoholic fatty liver disease • Offspring • Pregnancy

KEY POINTS

- Because preexisting or de novo nonalcoholic fatty liver disease (NAFLD) during pregnancy may increase the risk of maternal and offspring complications, it is plausible that metabolic-associated fatty liver disease (MAFLD) may cause similar or more severe adverse outcomes.
- Only a few studies evaluated the nexus between maternal MAFLD and its effects on pregnant women and newborns.
- More prospective studies are needed to evaluate the adverse clinical outcomes associated with MAFLD in pregnancy.

INTRODUCTION

Although the debate on the new nomenclature is still open, the new definition of metabolic-associated fatty liver disease (MAFLD), even in children, seems to fully reproduce the pathophysiologic aspects of liver disease that characterize nonalcoholic fatty liver disease (NAFLD), but undoubtedly brings out the need to take into careful consideration the metabolic aspects that fill the constellation of comorbidities associated with NAFLD.[1] Indeed, the new definition of MAFLD comprises the diagnosis of fatty liver confirmed by liver histology, imaging, blood biomarkers, or blood scores combined with at least one of other conditions. These conditions include excess adiposity, prediabetes, or type 2 diabetes mellitus, and two metabolic abnormalities, such as increased waist circumference, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol levels, impaired fasting glucose, and hypertension.[1]

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Endocrinol Metab Clin N Am 52 (2023) 521–531
https://doi.org/10.1016/j.ecl.2023.02.005 **endo.theclinics.com**

There is a scarcity of prospective epidemiologic studies after the new name (MAFLD) was adapted. However, a recent meta-analysis, which repurposes some existing epidemiologic data on fatty liver disease, found that the global prevalence of MAFLD is approximately 33% in the adult population, with varying distribution among the geographic areas.[2] Moreover, further meta-analyses estimated a MAFLD prevalence of 50.7% in the general population among overweight/obese adults, and of 44.94% in a special population based on data from pediatric obesity clinics.[3,4]

Recent retrospective studies in humans have investigated the prevalence of NAFLD during pregnancy highlighting that this condition may influence maternal and offspring outcomes, including gestational diabetes mellitus (GDM), gestational hypertension, caesarean delivery, preterm birth, preeclampsia, and abnormal fetal growth.[5–7] In particular, Sarkar and colleagues,[7] evaluating retrospectively data from a US database, reported that the prevalence of NAFLD in pregnancy increased in a timeframe of 9 years, with a rate of 10.5/100,000 pregnancies in 2007 and of 28.9/100,000 pregnancies in 2015. The authors also showed that metabolic comorbidities were more common in pregnant women with NAFLD where the risk of serious maternal and perinatal complications was significantly higher than in pregnant women with or without other chronic liver diseases. Similar results were confirmed in a study on 308,095 women registered in a Korean database, were NAFLD before pregnancy was strongly correlated with an increased risk of GDM.[8] Although all these clinical studies indicated that the adverse risks of obesity, metabolic syndrome, and NAFLD may affect maternal and perinatal outcomes, there are currently few lines of evidence whether the maternal MAFLD could be associated with more severe pregnancy-related complications in experimental mice models and humans.

In this review, we report all preclinical and clinical lines of evidence that may support the nexus between MAFLD and maternal and fetal outcomes during pregnancy, with an initial outline on the possible NAFLD murine models that may better recapitulate MAFLD.

PRECLINICAL MODELS FOR MATERNAL METABOLIC-ASSOCIATED FATTY LIVER DISEASE AND EFFECTS ON MATERNAL OUTCOMES DURING PREGNANCY

In the past, the development of a variety of dietary, genetic, chemical, and animal models of NAFLD have been established providing an invaluable tool for understanding the pathophysiologic mechanisms underlying the onset of NAFLD and its progression in terms of hepatic damage and metabolic dysregulation involving other organs.[9] These preclinical studies as described by Parthasarathy and colleagues,[10] have contributed to describe the so called “triadic lesion” concept that recapitulates the major hepatic features in NAFLD/nonalcoholic steatohepatitis (NASH), including hepatocyte injury, macrophage-mediated inflammation, and hepatic stellate cell activation, even if often the liver damage in animal models does not reach the severity observed in humans.

Currently, following the introduction of the new definition of NAFLD that shifts toward MAFLD, emphasis should be placed on the possibility to establish new models with an ability to fully mimic the systemic metabolic dysregulation and the hepatic injury occurring in the disease; or to use already available models for NAFLD/NASH, capable of reproducing the metabolic disorder emerging as dynamics-driven events into MAFLD. To date, there are no available models generated to resemble the MAFLD spectrum in humans, and most of the preclinical studies use animal models of NAFLD/NASH that also exhibit metabolic derangement.[11]

Table 1 summarizes the most suitable diet-induced obesity animal models (DIOs) for MAFLD and their characteristics.

Table 1
NAFLD models that recapitulate MAFLD

Type of DIOs Model	Type of Diet	Liver Damage	Dysmetabolic Phenotype
HFD	60% fat, 20% proteins, 20% carbohydrates	Complete spectrum of liver damage depending on time of diet regimen: steatosis in 10 wk and nonalcoholic steatohepatitis and fibrosis in >50 wk	Insulin resistance and hyperlipidemia in 10–12 wk
American lifestyle–induced obesity syndrome	45% calories in the chow from fat, 13% polyunsaturated fatty acids plus high-fructose corn syrup (55:45 wt/wt of fructose/glucose)	Complete spectrum of liver damage (hepatic steatosis, inflammation, and fibrosis) after 26 wk in mice	Obesity, metabolic syndrome, and dyslipidemia and insulin resistance after 16 wk in mice and 8 wk in rats
HFD and cholesterol	60% fat from cocoa butter and additional cholesterol (1.25% cholesterol and 0.5% cholate)	Complete spectrum of liver damage after 6–24 wk in mice	Oxidative stress and dyslipidemia, but not systemic insulin resistance

Abbreviations: DIO, diet-induced obesity; HFD, high-fat diet.

Among the animal models already established, those that best succeed in reproducing the full spectrum of hepatic and metabolic dysregulation occurring in MAFLD (eg, obesity, insulin resistance, and dyslipidemia) are those based on obesogenic DIO diets mainly developed in mice. The best studied DIO models are generally based on the administration of a regular high-fat diet (HFD). In particular, HFD with fat content up to 60% resulted usually in obesity and insulin resistance leading to a dysmetabolic phenotype after 10 to 12 weeks, including obesity, moderate hyperglycemia, hyperinsulinemia, and hypertriglyceridemia.[12] Mice fed an HFD develop a complete spectrum of liver damage, but it depends on the form and duration of the diet. Generally, they developed steatosis within 10 weeks, but it takes up to 36 weeks to develop hepatocyte ballooning and 52 weeks to NASH and fibrosis traits.[13]

However, several DIO models characterized by diets with different composition and types of sugars and fats have been established over time. Indeed, variations of the HFD composition with different type and ratio of carbohydrates and/or fat, such as additions of fructose or cholesterol in rodent DIOs, were found to be the most effective combination in mediating the more severe metabolic dysregulation and liver phenotype observed in humans.[13] According to a database of 3920 rodent models of NAFLD analyzed by a recent systematic review, the HFD/high-fructose diets were identified as the models that most closely resemble the human phenotype of NAFLD.[14] In fact, the American lifestyle–induced obesity syndrome diet composed of 45% calories (chow standard diet) from fat, 13% polyunsaturated fatty acids (PUFAs), with addition of high-fructose corn syrup (55:45 wt/wt of fructose/glucose) was found to affect metabolic systems in mice and rat models. More specifically, American lifestyle–induced obesity syndrome diet in mice was reported to promote obesity, metabolic syndrome, dyslipidemia, and insulin resistance after 16 weeks, and features of hepatic steatosis, inflammation, and fibrosis after 26 weeks. Similar metabolic dysfunction has been reported in rat models after only 8 weeks of treatment.[15]

The combination of HFD (60% fat from cocoa butter) and cholesterol supplementation (1.25% cholesterol and 0.5% cholate) was able to induce a more rapid and severe development of liver phenotype associated to NAFLD accompanied by metabolic disorders. After 6 to 24 weeks, steatosis, histologic NASH (inflammation, hepatocellular ballooning) features, and F1-F2 fibrosis were observed, whereas F3 fibrosis was appreciable only after 24 weeks.[16,17]

Experimental studies based on the previously described models highlighted that maternal overnutrition during pregnancy may lead to phenotypic changes in offspring, thus resembling human MAFLD.[18]

In most studies, the effect on the liver and on metabolic dysregulation were not investigated together. In mice during pregnancy, HFD may cause fatty liver and eventually liver fibrosis, changes in body composition, increased visceral adiposity, dyslipidemia, insulin resistance, reduced glucose tolerance related to reduced β-cell mass, and GDM.[18,19] A pattern of metabolic disorders more evident in mothers was instead observed in mouse models treated with a diet rich in fat and sucrose, where the NAFLD pattern could be associated with a state of low-grade systemic inflammation that may lead to MAFLD features.[18–20]

EFFECT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE ON MATERNAL OUTCOMES DURING PREGNANCY: CLINICAL EVIDENCE

NAFLD is nowadays considered as an independent risk factor for hypertensive complications, postpartum hemorrhage, and preterm birth. It is mandatory that NAFLD

should be considered a high-risk obstetric condition, with clinical implications for counseling about potential obstetric complications and appropriate pregnancy care.[7]

The association between MAFLD and negative maternal outcomes during pregnancy was only recently reported in humans. Indeed, Lee and colleagues[21] have recently tried to define the risk of pregnancy complications according to the definitions of NAFLD and MAFLD by secondary analysis of a multicenter prospective cohort. The authors found that pregnant women with MAFLD exhibited the highest risk of adverse pregnancy outcomes including GDM, hypertension, and caesarean delivery compared with those with NAFLD without metabolic dysfunction. These results highlight that a preexisting maternal metabolic derangement may play a central role in the pathogenesis of adverse pregnancy outcomes, and that fatty liver may have an additive effect by triggering same or different pathways associated with these adverse outcomes. Systemic inflammation driven by obesity, insulin resistance, and NAFLD could be the detrimental mechanism that leads to adverse outcomes in pregnant women, such as preeclampsia.[22]

An inverse association of prolonged breastfeeding with the prevalence of NAFLD and metabolic alterations in middle age including body mass index (BMI), insulin resistance, elevated triglyceride levels, and waist circumference was also observed in women from the Coronary Artery Risk Development in Young Adults cohort.[23]

The mother's metabolic phenotype associated to a MAFLD pattern could be relevant in changes at the level of gut microbiota composition, which in turn may affect maternal insulin sensitivity and secretion during pregnancy.[24]

RESEARCH EVIDENCE ON THE EFFECTS OF MATERNAL METABOLIC-ASSOCIATED FATTY LIVER DISEASE ON OFFSPRING OUTCOMES

Because most of the obesogenic diets may affect offspring phenotype, several experimental models have described their effects including alterations in fetal growth, obesity, NAFLD, altered pancreatic β-cell mass, insulin resistance, and hypertension.[18]

Studies in several models, including those in mice, support the developmental programming of weight gain and metabolism in the offspring, demonstrating that obesogenic diets during pregnancy can transmit a propensity for adiposity, glucose intolerance, and cardiovascular dysfunction to the newborn.[25,26] However, most studies in mice were conducted by investigating the effect of maternal obesogenic diets before and during pregnancy and lactation on offspring weight gain, fatty liver, and dysmetabolism.[27,28]

A study investigating the effects of consumption of HFD in utero and during lactation reported excessive body weight, and the presence of fatty liver and insulin resistance in the offspring.[26] Moreover, Marin and colleagues[27] reported that in juvenile male mice fed with HFD plus fructose in the drinking water, the progression of liver damage and NASH development is faster than in juvenile female mice.

The role of maternal diet on offspring metabolic balance was well evaluated by de Paula Simino and colleagues.[28] The authors showed that in female mice on HFD, overnutrition during gestational and lactation periods disrupted lipid and glucose metabolism affecting glucose tolerance and insulin sensitivity in newborn by modifying the expression of hepatic miRNAs associated with insulin resistance and NAFLD. In addition, these changes increased the offspring susceptibility to obesity and metabolic derangement in adult life.

In female mice fed with a normal-fat diet or HFD for 12 weeks before conception and then during pregnancy and lactation, it was observed that appropriate dietary interventions initiated sufficiently early before pregnancy and continued also during

lactation reduced the risk of offspring developing MAFLD even after the exposure to a maternal HFD.[29]

Animal experiments observed that maternal exposure to HFD during pregnancy and lactation could have lasting effects on increasing insulin resistance, associated with hepatic inflammation even in offspring with normal weight.[30]

There are several mechanisms that may link maternal DIO phenotype to offspring changes, including oxidative stress, epigenetic regulation of gene transcription, and changes in microbiota composition.[30–32] Indeed, maternal HFD caused metabolic dysfunction, including altered liver growth and oxidative stress thus contributing to NAFLD and the alteration of cholesterol levels in offspring.[30] Moreover, it has been reported that HFD consumption may induce epigenetic regulation of important genes involved in fatty acid oxidation and oxidative phosphorylation via DNA methylation modifications.[31] Wankhade and colleagues[32] demonstrated that even though HFD consumption in mice caused a strong alteration of the gut microbiome composition, the effects on weight gain, fatty liver, and metabolic dysfunction were dominant only in the male offspring.

A recent systematic review that investigated the metabolic repercussions of maternal exposure to HFD on offspring reported that exposures prepregnancy and during pregnancy and/or lactation was associated with increased body weight, food intake, and body adiposity in young and adult offspring.[33]

CLINICAL EVIDENCE ON THE EFFECT OF MATERNAL METABOLIC-ASSOCIATED FATTY LIVER DISEASE ON PROGENY

In addition to the evidence in mice models, a large number of clinical studies suggest that children born of pregnancies characterized by obesity or related GDM exhibited an increased risk of obesity, increased adiposity, impaired glucose tolerance, NAFLD, and other metabolic derangements.[34,35] Moreover, several studies highlighted how the mother's lifestyle and obesity during pregnancy can influence the short- and long-term metabolic pathways of the newborn child.[36] Hence, a clinical score has been proposed to calculate the risk of obesity based on the first thousand days of life.[37]

Cinelli and colleagues[38] evaluated the relationship between maternal and offspring (cord-blood) erythrocyte fatty acids at birth, in relation to prepregnancy BMI and gestational weight gain. The study showed that prepregnancy BMI but not gestational weight gain was correlated with changes in lipid profile in fetus including percentage of PUFAs, omega-6 fatty acid, and docosahexaenoic acid. The same authors demonstrated that the content of omega-3 PUFAs of maternal dietary intake during pregnancy influences the offspring DNA methylation profile, finding a correlation between erythrocytes membrane PUFA content and epigenetic regulation in offspring cord blood. In particular, it has been found that four genes (*MSTN*, *IFNA13*, *ATP8B3*, and *GABBR2*) mainly involved in the insulin resistance and adiposity development and phospholipid translocation across cell membranes were differentially methylated, among low, medium, and high omega-3 PUFA maternal intake groups.[39]

Furthermore, metagenomics studies have reported the possible maternal-fetal transmission of the intestinal microbiota, mainly characterized by *Bifidobacterium* and *Bacteroides*, during pregnancy and breastfeeding.[40] Infants receiving exclusive breast milk exhibited an increase in some taxa, such as *Bifidobacterium* and *Lactobacillus* spp, in respect to the formula-fed infants that showed high levels of *Firmicutes*.[41] This could be a reasonable explanation for the protective effect of breastfeeding on the subsequent development of NAFLD.[42] Breastfeeding also reduces the risk of MAFLD in mothers.[43]

GDM alone and together with maternal overweight/obesity impacts colonization of infant's gut influencing the amount of several taxa thus favoring a microbiome profile that could be associated with future risk of the metabolic dysregulation and MAFLD in childhood.[44–46] Moreover, children of obese women showed an increased risk to have MAFLD in adolescence.[34] This evidence was reinforced by a study demonstrating that children exposed in utero to maternal MAFLD may be more likely to exhibit early obesity and MAFLD.[47]

Unfortunately, the number of studies evaluating MAFLD and fetal outcomes is extremely small compared with those reported on NAFLD and extensively described by Fouda and colleagues.[6]

A study focused on the relationship between breastfeeding duration, breast milk composition, maternal obesity, and their effects on the rate of NAFLD during adolescence.[48] In particular, the study reported that high prepregnancy BMI correlates with less than 6 months of exclusive breastfeeding, which in turn is associated with a significantly increased risk of NAFLD in late adolescence and adverse metabolic profile. However, a similar study based on the Avon Longitudinal Study of Parents and Children (ALSPAC), while confirming the impact of maternal prepregnancy BMI on NAFLD development in the offspring, does not provide evidence regarding the protective role of exclusive breastfeeding greater than or equal to 6 months on NAFLD in young adulthood.[49] These last lines of evidence shed light on the relevance of lifestyle changes to prevent MAFLD in such children born to mothers with the disease.

MANAGEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE IN PREGNANCY

The management of MAFLD in pregnancy includes early diagnosis, and a comprehensive medical support to carry out preventive measures and nutritional approaches that may reduce the risk of MAFLD-related adverse outcomes.[6] In these conditions, preconception counseling and an appropriate nutritional management during pregnancy are recommended.

Obese women with preexisting MAFLD should be monitored during pregnancy for high-risk obstetric complications, such as the exacerbation of already existing pathologies, hypertension, bleeding after delivery, and preterm birth.[6] Moreover, a baby who is born to a mother with MAFLD should be considered at risk of MAFLD during childhood. Breastfeeding and healthy weaning should be strongly promoted.[42,43] In these children, clinical and auxologic parameters must be closely monitored over time to suspect MAFLD early, possibly looking for biochemical abnormalities, such as reduced glucose tolerance, dyslipidemia, and alteration of liver function tests. Because there is no currently approved pharmacotherapy for MAFLD management in pregnancy, the treatment is mainly by lifestyle interventions, such as healthy diet and appropriate physical activities permitted during pregnancy.

SUMMARY AND FUTURE DIRECTIONS

MAFLD, the term proposed to substitute NAFLD, includes not only the hepatic manifestation of a multisystem disorder but also the associated metabolic dysfunction. There is currently inadequate clinical evidence showing that similar to NAFLD, maternal MAFLD can exist before pregnancy or can develop de novo during pregnancy thus influencing clinical outcomes in pregnant women and newborns. This limitation could be linked to the high heterogeneity that characterizes MAFLD, thus making the reproduction of laboratory evidence of systemic metabolic dysregulation and hepatic injury difficult in experimental models.

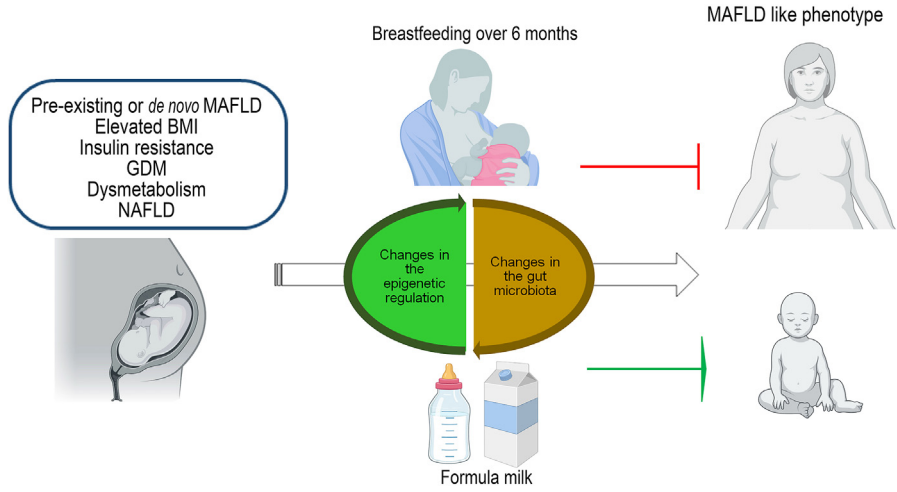

Fig. 1. Potential effects of preexisting or de novo maternal NAFLD and its associated metabolic dysregulation on MAFLD outcome in the pregnant woman and newborn. (Created with BioRender.com.)

However, based on the reported findings, metabolic adaptation caused by epigenetic remodeling of gene expression and/or microbiota composition could play a central role in pregnancy outcomes. Changes in epigenetic regulation that could be inherited, and alterations in the gut microbiome during fetal life may affect the metabolic response of the mother and child in animal models and humans (Fig. 1).[50] These metabolic changes are potentially reversible if unhealthy diet and adverse lifestyle are corrected during pregnancy, and by encouraging breastfeeding or the use of appropriate formula milk in the postpartum period.

CLINICS CARE POINTS

- MAFLD has emerged as a major health challenge in recent years because of the global obesity pandemic.
- Epigenetic, genetic, and environmental factors, such as adverse lifestyles, alterations in gut microbiome, and breastfeeding, may impact maternal and fetal outcomes in relation to MAFLD.
- Because there is no currently approved pharmacotherapy for MAFLD, and the difficulty in performing clinical trials among pregnant women, management of the disease during pregnancy is mainly by lifestyle interventions along with encouraging breastfeeding during the postpartum period.
- Obese women with dysmetabolism, GDM, or MAFLD should be monitored during pregnancy for high-risk obstetric conditions, such as the exacerbation of already existing pathologies, hypertension, bleeding after delivery, and preterm birth.
- A baby who is born to a mother with MAFLD should be screened as early as possible also for fatty liver by hepatic function tests and abdominal ultrasound.
- In these conditions, preconception counseling and accurate nutritional management during pregnancy can help avoid adverse maternal and offspring clinical outcomes.

DISCLOSURE

No conflict of interest.

FUNDING

This work was supported by the Italian Ministry of Health with "5x1000 2022".

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