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Review

Metabolic-associated fatty liver disease and pregnancy complications: new challenges and clinical perspectives

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***Abstract*:** The term metabolic-associated fatty liver disease (MAFLD), with a global prevalence estimated at 38.77%, has gradually replaced the traditional concept of non-alcoholic fatty liver disease (NAFLD). Compared to the general population, the incidence of MAFLD is notably higher among pregnant women, posing potential risks to both maternal and neonatal health. This review summarizes the latest research on MAFLD, focusing on its association with pregnancy complications. Additionally, it provides a comparative analysis with previous studies on NAFLD, presenting a comprehensive perspective for clinical management. Findings suggest that pregnant women with MAFLD face a higher risk of gestational hypertension and cesarean delivery compared to those with NAFLD, while the risk for gestational diabetes mellitus remains similar between the two conditions. Additionally, MAFLD is associated with an increased likelihood of delivering large-for-gestational-age infants and heightened risks of preterm birth and low birth weight. Current treatment strategies for MAFLD focus on lifestyle modifications, such as dietary adjustments and increased physical activity. However, there is an urgent need for the development of safe and effective pharmacological treatments, particularly tailored toward pregnant women. Future research should delve deeper into the causal relationships between MAFLD and pregnancy complications and explore optimal therapeutic approaches to improve outcomes for mothers and their infants.

Plain language summary

Metabolic-associated fatty liver disease and pregnancy complications

Metabolic-associated fatty liver disease (MAFLD) is a new term for what used to be called non-alcoholic fatty liver disease, affecting nearly two-fifths of people worldwide. It's especially concerning for pregnant women, as it can cause serious problems for both the mother and the baby. This summary looks at the latest studies on how MAFLD affects pregnant women and how it compares to the older diagnosis of NAFLD. The findings show that pregnant women with MAFLD are more likely to have high blood pressure during pregnancy and need a cesarean section. However, the chance of getting gestational diabetes is about the same for both MAFLD and NAFLD. MAFLD also increases the risk of having a baby that is too large for its gestational age, as well as the risks of preterm birth and low birth weight. Right now, the main way to treat MAFLD is through healthy lifestyle changes like diet and exercise. But there's a big need for new medicines that are safe for pregnant women. Future studies should look more into how MAFLD causes complications during pregnancy and find the best ways to treat it to help mothers and their babies.

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Introduction

Recently, an international expert consensus has proposed the term metabolic-associated fatty liver disease (MAFLD) as a more precise and updated definition to replace non-alcoholic fatty liver disease (NAFLD). The new nomenclature underscores the metabolic dysregulation associated with NAFLD, reduces stigma, and offers fresh perspectives for the diagnosis and treatment of the disease.[1,2] The global prevalence of MAFLD is as high as 38.77%,[3] surpassing previous estimates of NAFLD's global prevalence (29.62%),[4] suggesting that MAFLD may affect nearly two-fifths of the global population. As understanding of MAFLD deepens, its prevalence among pregnant women has nearly doubled in recent years[5]—a trend that not only raises clinical concerns but also poses a public health challenge. While prior research has revealed potential links between NAFLD and pregnancy complications,[6–8] given MAFLD's high prevalence worldwide and its potential effects, it is crucial to further investigate the connections between MAFLD and pregnancy complications.

Furthermore, MAFLD not only affects women's health during pregnancy but also has long-term consequences for neonatal health, such as metabolic issues in childhood and health risks in adulthood.[9,10] This review aims to compile and analyze the latest research on MAFLD, specifically its relationship with pregnancy complications, and compare it with previous studies related to NAFLD. Through this comparison, we aim to provide clinicians with comprehensive information for the effective management of MAFLD in pregnant patients and suggest future research directions.

Diagnosis of MAFLD: Non-invasive approaches

Liver biopsy is the gold standard for the diagnosis of MAFLD.[11,12] However, because of its invasive nature and the potential risks it poses to pregnant women, non-invasive diagnostic modalities have become the focus of current research (Table 1). These methods encompass conventional imaging techniques such as ultrasonography, CT scans, and MRI, as well as algorithm-based scoring systems such as the hepatic steatosis index (HSI) and the MAFLD fibrosis score (MFS). A significant breakthrough in traditional diagnostic methods was achieved by Kaposi et al. with the development of a nonlinear regression model based on quantitative ultrasound technology.[13] This model predicts ultrasound-estimated fat fraction and provides a non-invasive assessment of liver fat content, demonstrating its potential as an ideal screening tool for NAFLD and MAFLD.[13] Cheung et al. developed and validated the MFS and demonstrated that it outperformed existing non-invasive scoring methods in determining the presence of advanced fibrosis in patients with MAFLD.[14] Okada conducted a study with participants from a high-volume center in Tokyo to evaluate the efficacy of three markers of fatty liver, namely the fatty liver index (FLI), the HSI, and the lipid accumulation product, along with three common metabolic markers, namely waist-to-height ratio, body mass index (BMI), and waist circumference (WC), in predicting the diagnostic ability for MAFLD.[15] These markers were found to be accurate predictors of MAFLD, and FLI and HSI showed high predictive accuracy in all subgroups studied.[15] In a study focusing on the Uighur adult population in Kashgar, Xinjiang, China, FLI and BMI showed high accuracy in screening for MAFLD, outperforming other assessment indices.[16] Zou compared the effectiveness of 12 non-invasive scores in diagnosing MAFLD and found that triglyceride glucose-BMI (TyG-BMI)[17] had satisfactory diagnostic performance in identifying individuals at high risk for MAFLD in the western regions of China. In contrast, in the American population, TyG-WC[18] showed the best ability to identify MAFLD risk.[19]

These research results emphasize the importance of selecting appropriate non-invasive scoring models, especially taking into account the characteristics of different regions and ethnic groups. Overall, these non-invasive methods have

Table 1. Comparison of diagnostic methods for MAFLD.

Diagnostic method	Description	Advantages	Disadvantages
Liver biopsy[20]	A procedure where a small sample of liver tissue is collected for microscopic examination.	Gold standard; provides accurate assessment of liver damage and type.	Invasive with risk of complications such as bleeding; not suitable for repeat examinations.
Ultrasonography[21]	High-frequency sound waves are used to create an image of the liver.	Non-invasive, radiation-free, low cost, widely used for initial screening.	Low sensitivity for mild to moderate steatosis; operator-dependent; does not provide information on the degree of fibrosis.
CT[22]	Computer-processed X-rays to produce cross-sectional images of the liver.	Non-invasive, fast, can detect other liver abnormalities, high sensitivity and specificity for moderate to severe steatosis.	Low sensitivity for early-stage fatty liver, radiation exposure.
MRI[23]	Magnetic fields and radio waves are used to create detailed images of the liver.	Non-invasive, no radiation, accurate assessment of liver fat content and fibrosis.	High cost, longer examination time, not suitable for some patients (e.g. those with pacemakers).
Hepatic steatosis index[24]	An algorithm combining AST/ALT ratio, BMI, gender, and diabetes status.	Non-invasive, simple calculation, high sensitivity for excluding MAFLD.	Low specificity for diagnosing MAFLD.
Fibrosis-4 index[25]	An algorithm combining age, serum transaminase levels, and platelet count.	Non-invasive, allows for risk stratification of liver fibrosis, and predicts liver-related morbidity and mortality.	Less reliable for identifying advanced fibrosis, sensitivity, and positive predictive value are limited.
MAFLD fibrosis score[14]	A score developed using machine learning to combine clinical and laboratory measures for assessing advanced fibrosis risk in MAFLD patients.	Provides generality and validation, statistical power to independently predict advanced fibrosis.	Potential selection bias, concerns about interpretive consistency, and limited accuracy in different settings.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; MAFLD, metabolic-associated fatty liver disease; MRI, magnetic resonance imaging.

demonstrated good diagnostic performance in non-pregnant populations and offer new opportunities for the safe diagnosis and effective management of MAFLD during pregnancy. However, due to the unique physiological conditions of pregnancy, further research is needed to explore and confirm their applicability and accuracy in pregnant women.

The role of genetic and epigenetic factors in MAFLD and pregnancy complications

As research on the pathophysiological mechanisms of MAFLD advances, mounting evidence indicates that genetic and epigenetic factors play a pivotal role in the development of MAFLD and its complications during pregnancy. To date, more than 10 single-nucleotide polymorphisms (SNPs) associated with the risk of MAFLD have been identified, and these involve genes such as PNPLA3, TM6SF2, and MBOAT7.[26–28] Among them, several classic SNPs in PNPLA3 and TM6SF2 have been repeatedly confirmed in numerous independent studies, and their effects have also been discussed thoroughly. For example, specific SNPs within the PNPLA3 gene are associated with increased hepatic lipid accumulation, exacerbating sensitivity to the toxicity of agents such as ethanol and methotrexate.[29,30] Mutations in the TM6SF2 gene affect the

secretion of very-low-density lipoprotein, thereby increasing the risk of hepatic steatosis and fibrosis and potentially accelerating the progression to hepatocellular carcinoma (HCC).[31,32] Recent studies have also identified novel SNPs associated with MAFLD, further improving the understanding of the pathogenesis of hepatic steatosis.[33]

Regarding epigenetic mechanisms, regulatory processes such as DNA methylation, histone modifications, non-coding RNA regulation, and RNA methylation play a crucial role in the progression of MAFLD. Currently, DNA methylation is the most extensively investigated epigenetic mechanism, with studies revealing its close association with MAFLD.[34] For example, recent investigations have suggested that hypermethylation of mitochondrial DNA may impair mitochondrial gene expression and metabolic function, thereby facilitating lipid accumulation—a process that plays a key role in the pathogenesis of MAFLD.[35] Beyond DNA methylation, histone modifications stand as a significant determinant in the advancement of MAFLD. Histones, the fundamental protein constituents of nucleosomes, undergo a multitude of post-translational modifications at their N-terminal amino acid tails, including acetylation, methylation, phosphorylation, SUMOylation, ubiquitination, and ADP-ribosylation.[36] Particular attention has been paid to histone acetylation and methylation because of their significant influence on gene expression and cellular functions. For example, the nuclear receptor subfamily 2, group F, member 6 (NR2F6) is capable of directly binding to the promoter region of the CD36 gene in hepatocytes. Such binding not only facilitates the recruitment of nuclear receptor coactivator 1 (SRC-1) but also enhances the acetylation levels of histones in that region, thereby promoting hepatic lipid accumulation.[37] In addition to acetylation, the role of methyltransferases such as Jumonji domain-containing protein 2B (JMJD2B) in MAFLD has garnered research interest. Through its direct effect on the histone 3 lysine 9 (H3K9) level, JMJD2B has been shown to play a significant role in the lipogenesis pathway of MAFLD. The enzymatic activity of JMJD2B can remove the trimethylation and dimethylation marks of H3K9, leaving a monomethylation mark, which can trigger the activation of peroxisome proliferator-activated receptor gamma 2 (PPARG2) and its target genes, thereby increasing hepatic lipid synthesis.[38] However, despite progress in understanding histone acetylation and methylation, the roles of other types of histone modifications in MAFLD, such as phosphorylation, SUMOylation, and ubiquitination, remain elusive.

Despite initial advances in delineating the genetic and epigenetic underpinnings of MAFLD, the intricate mechanisms through which these factors modulate pregnancy-related complications have not been fully elucidated. Further research is essential to clarify the precise roles that these genetic and epigenetic determinants play in shaping maternal and neonatal health during gestation, as well as their influence on the spectrum of pregnancy outcomes.

Risk factors of MAFLD

MAFLD is closely associated with a broad spectrum of metabolic dysregulation. Compared to NAFLD, MAFLD is significantly associated with male gender, higher BMI, hypertension, diabetes, dyslipidemia, and higher fibrosis scores.[39] Specifically, being overweight and obese is the major risk factor for MAFLD.[12]

A large-scale meta-analysis of more than 4 million patients with MAFLD found a mean BMI of 27.71 kg/m² and a mean WC of 92.91 cm among these individuals.[3] Studies in the overweight and obese population have shown that the global prevalence of MAFLD in overweight or obese adults is as high as 50.7% (95% CI, 46.9–54.4).[40] In addition, hypertension and diabetes are common risk factors in individuals with MAFLD, with the meta-analysis showing prevalence rates of 43.72% for hypertension and 22.79% for diabetes in this cohort.[3] According to a recent systematic review of 49,419 patients with type 2 diabetes from 20 different countries, the global prevalence of MAFLD among individuals with type 2 diabetes is estimated to be greater than 50%.[41]

Clinical guidelines for MAFLD in the Asia-Pacific region even classify individuals with overweight/obesity and type 2 diabetes as high-risk groups. In particular, dyslipidemia—especially elevated triglycerides and low levels of low-density lipoprotein cholesterol—is a significant risk factor for the development of MAFLD.[2] In Lee's cohort study, it was reported that 42.72% of

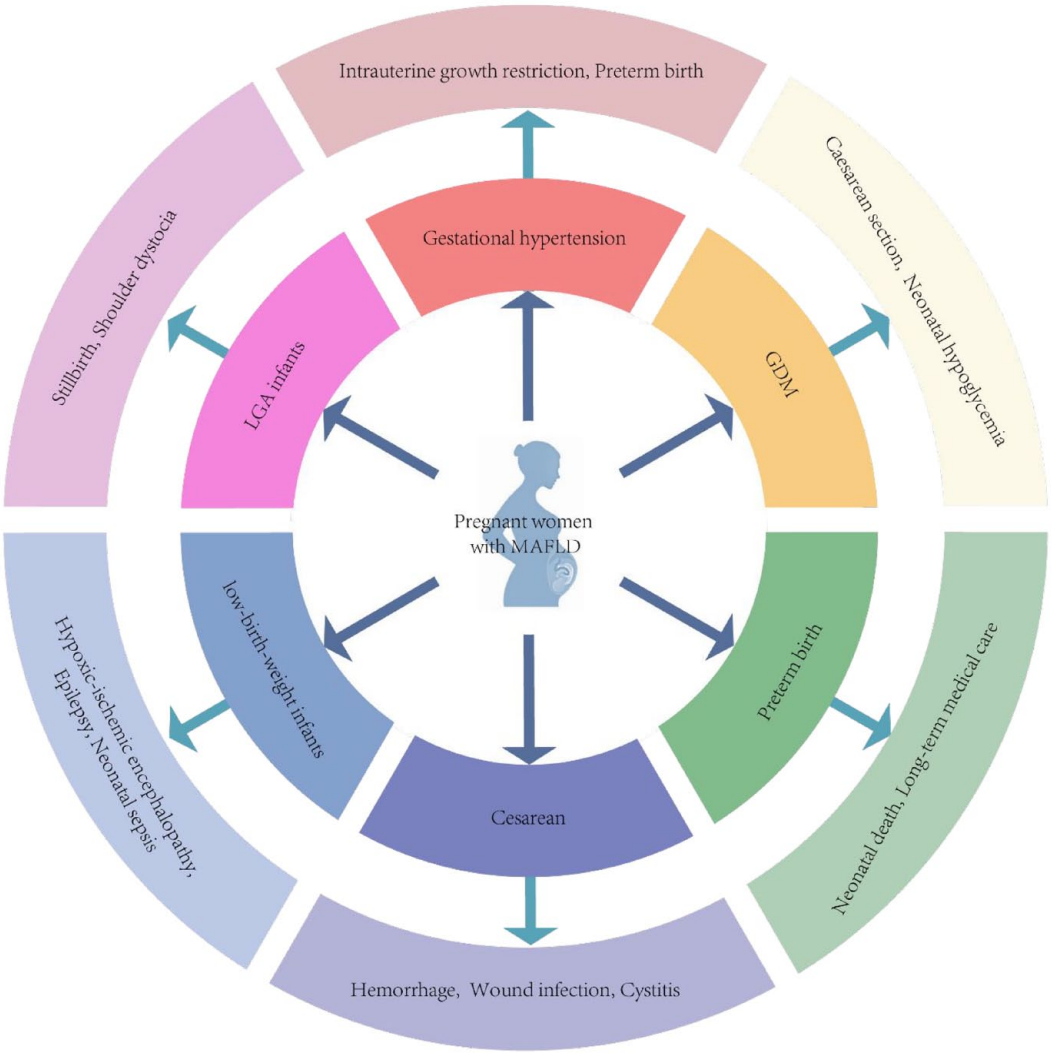

Figure 1. MAFLD-associated gestational complications and their impact on neonatal health. This chart provides a detailed representation of gestational complications with MAFLD.
GDM, gestational diabetes mellitus; LGA, large for gestational age; MAFLD, metabolic-associated fatty liver disease.

patients with MAFLD had low levels of high-density lipoprotein cholesterol.[42] The pathophysiological underpinnings of these metabolic abnormalities are often due to insulin resistance—a common denominator induced by an imbalance between energy intake and energy expenditure, leading to decreased insulin responsiveness in multiple tissues—and alterations in the gut microbiota,[43–45] which in turn promote hepatic steatosis.[46]

The impact of these metabolic abnormalities is not confined to the patients alone; they may also pose a risk to maternal health during pregnancy and affect neonatal development (Figure 1). Consequently, it is important to continue investigating the primary risk factors of MAFLD, particularly how MAFLD affects the risk of pregnancy complications, and to explore effective prevention strategies.

The role of the gut microbiome in MAFLD

The gut microbiome, a complex ecosystem within the human body comprising approximately 100 trillion microorganisms, is considered a virtual metabolic and endocrine organ.[47] These microorganisms directly participate in the host's energy

balance and metabolic health by influencing the absorption of nutrients and the production of metabolic byproducts. In MAFLD, the role of the gut microbiome is particularly critical.[48] The gut–liver axis serves as a vital connection between the gastrointestinal tract and the liver, facilitating interaction through the portal vein system.[49] Microorganisms entering the liver via the portal vein can influence bile acid synthesis and metabolism, production of pro-inflammatory factors, and intestinal barrier function, potentially triggering hepatic inflammation and fibrosis, thereby promoting the progression of MAFLD and its severe form, non-alcoholic steatohepatitis.[49–52]

During pregnancy, significant physiological and metabolic changes occur, including alterations in the composition and function of the gut microbiome. These changes can significantly affect maternal health and pregnancy outcomes by modulating energy metabolism and immune responses.[53,54] While research on the gut microbiome's role in MAFLD during pregnancy is sparse, studies on gestational diabetes mellitus (GDM) offer insights into metabolic dysregulation that may have implications for MAFLD. For example, a previous study reported abnormal fluctuations in the levels of specific gut microbiota components, such as *Faecalibacterium prausnitzii*, in patients with GDM, suggesting that shifts in certain bacterial populations in the gut microbiome of pregnant women may be linked to an increased risk of GDM.[55] Since GDM is closely associated with metabolic abnormalities, this condition may exacerbate the development of MAFLD.

In newborns, the maternal gut microbiome plays a critical role in colonizing their gut microbiota.[56] It has been shown that the state of the maternal gut microbiome, especially at the time of delivery, can significantly influence the diversity and composition of the newborn's microbiota, which are crucial for the development of the infant's immune system and long-term health.[57,58] Previous studies have substantiated that infants born to mothers with GDM exhibit significant differences in the diversity and composition of gut microbiota compared with those born to mothers without GDM. The microbiota of GDM infants show lower α-diversity, and at the phylum level, there is an increased relative abundance of *Proteobacteria* and *Actinobacteria*, while *Bacteroidetes* are significantly reduced.[59] These findings imply that maternal metabolic disorders can affect neonates through the vertical transmission of shifts in the gut microbiome, thereby potentially influencing the child's future health.[60,61]

Therefore, in-depth research into the role of the gut microbiome in non-pregnant women, pregnant women, and newborns—particularly how it affects the risk and progression of MAFLD—is crucial for developing targeted prevention and treatment strategies. Such studies not only help us understand the complex functions of the gut microbiome but also reveal new intervention points to reduce the occurrence of MAFLD and its associated complications.

MAFLD and pregnancy complications

MAFLD and gestational hypertension

Gestational hypertension is a common complication in pregnant women. Its incidence has increased by 25% over the past two decades, a trend that is likely to continue.[62] This complication not only increases the risk of intrauterine growth restriction, placental abruption, preterm birth, and cesarean section, but it may also have long-term effects on maternal and infant health.[63] In this context, the influence of MAFLD, a recently defined disease, on gestational hypertension has attracted the attention of researchers. Numerous studies have shown a notable association between MAFLD and gestational hypertension.[64] Specifically, a meta-analysis has highlighted that pregnant women with MAFLD are 3.27 times more likely to experience pregnancy-associated hypertension compared with those without MAFLD.[65] In a 2021 study, a prospective cohort analysis of 1744 pregnant women indicated that those with MAFLD had a 2.69-fold increased risk of gestational hypertension compared with patients without the condition.[66] Additionally, a meta-analysis focusing on pregnancy outcomes related to NAFLD indicated that women with NAFLD were 1.83 times more likely to develop gestational hypertension than those without NAFLD, suggesting a lower risk profile compared with MAFLD.[67]

MAFLD and GDM

Given that GDM is a known risk factor for type 2 diabetes, it is plausible that they share similar metabolic risk factors, such as MAFLD. It has

been indicated that the detection of MAFLD during pregnancy through liver ultrasound can correspondingly increase the risk of GDM in women. In a 2022 study, Lee categorized 762,401 women into four groups, namely non-fatty liver disease (FLD), NAFLD only, MAFLD only, and both FLD conditions. Compared with women from the non-FLD cohort, those diagnosed with FLD exhibited a heightened risk of adverse pregnancy outcomes and cesarean delivery, with this risk being particularly accentuated in women with MAFLD. Specifically, women with MAFLD alone had a 2.88-fold higher risk of GDM than those without any FLD.[42] This association may be mediated by obesity—a closely linked condition to MAFLD and a known risk factor for GDM.[65] Fei et al. conducted a cohort study utilizing FibroScan® to assess 50 pregnant women and found that 32.0% developed GDM according to the Australasian Diabetes in Pregnancy Society diagnostic criteria. Among these women, 50.0% who had been initially diagnosed with MAFLD later developed GDM—a difference that was not statistically significant ($p = 0.37$) compared with women with normal liver assessments (29.5%)—but the trend was noteworthy.[68] A multiethnic cohort study involving 108 GDM pregnant women showed that those with MAFLD had higher BMI, parity, and blood pressure than women with normal liver assessments and were more likely to require insulin therapy during FibroScan® assessment.[69] These MAFLD patients also had higher peaks in insulin dosage requirements, suggesting abnormalities in insulin metabolism, including decreased insulin sensitivity and impaired β-cell function, which may be related to the onset of GDM and difficulties in blood glucose control. Current findings on MAFLD are consistent with previous observations on NAFLD, indicating a clear link between hepatic fat deposition and GDM. A meta-analysis encompassing seven studies showed that the incidence of GDM in women with NAFLD was 26.0%, nearly three times higher than the risk in non-NAFLD women,[70] a situation that mirrors that of pregnant women with MAFLD. In summary, the relationship between MAFLD and GDM is complex. MAFLD may increase the risk of GDM, while the occurrence of GDM may exacerbate the severity of MAFLD, thereby influencing its treatment and management. Although the concept of MAFLD provides a new perspective for understanding, the coexistence of these two conditions still requires comprehensive clinical consideration. Future research needs to investigate the interplay between MAFLD and GDM and seek ways to improve treatment and prevention for this particular population.

The link between MAFLD and pregnancy complications is mediated by the pivotal role of obesity

A recent study assessing postpartum hepatic steatosis and liver stiffness has demonstrated a correlation between pre-pregnancy overweight and obesity, as well as chronic hypertension, with significant hepatic steatosis or controlled attenuation parameter (CAP) values exceeding 300 dB/m. However, GDM, preeclampsia, and gestational hypertension were not associated with CAP values reaching 300 dB/m.[71] These findings further substantiate the link between obesity and the interplay of MAFLD and pregnancy complications. With the global rise in obesity rates, particularly among women of childbearing age, maternal obesity during pregnancy has emerged as a significant factor in maternal and infant health.[72] Previous studies have shown that, compared with women of normal weight, obese women have higher rates of miscarriage and stillbirth.[73] A retrospective cohort study further revealed that pre-pregnancy obesity in women was associated with a 1.49-fold and 1.64-fold increased risk of cesarean delivery and preeclampsia, respectively, compared with women of normal weight.[74] Additionally, the offspring of overweight and obese women are at a higher risk of myocardial dysfunction,[75] and with every 5–7 kg/m^2 increase in pre-pregnancy BMI, the risk of preeclampsia doubles.[76] It is noteworthy that central obesity (abdominal fat) may have a stronger association with MAFLD than generalized obesity due to its closer link to metabolic abnormalities and cardiovascular risk.[77] This may explain the higher prevalence of central obesity among patients with MAFLD and underscores the importance of weight management during pregnancy in preventing both MAFLD and pregnancy complications. While obesity is a key risk factor for MAFLD, the two are not entirely related. The development of MAFLD is related to a variety of factors, including genetics, diet, lifestyle, and environmental factors, and the condition encompasses both non-obese (lean MAFLD) and obese (obese MAFLD) phenotypes.[77] This suggests that MAFLD and obesity may independently affect pregnancy outcomes.

In conclusion, although current research provides an initial understanding of the impact of MAFLD and obesity on the health of pregnant women and their offspring, further studies are needed to delve deeper into this area.

MAFLD and mode of delivery

It has been suggested that MAFLD may be associated with an increased risk of cesarean delivery, which can be accompanied by a range of complications such as hemorrhage, wound infection, cystitis, endometritis, hematoma, and the potential need for additional surgical interventions, thereby affecting the health of the mother and newborn.[78] Research conducted in 2021 showed that the likelihood of cesarean delivery was 1.87 times higher in women with MAFLD than in those without the condition.[66] A meta-analysis from the same year corroborated these results, showing a 2.78-fold increase in the risk of cesarean delivery for women with MAFLD relative to the control group.[65] Further research in 2022 indicated that this risk was 2.36 times greater in women with MAFLD alone than in those without FLD and 1.96 times higher compared with those with only NAFLD, reinforcing the association between MAFLD and cesarean delivery.[42] Compared with previous conclusions on NAFLD, the risk of cesarean delivery in MAFLD is notably increased. Given these risks, in clinical practice, careful consideration of the indications for cesarean delivery is necessary for pregnant women with MAFLD, along with appropriate preventive and management measures.

MAFLD and neonatal outcomes

Lee's investigation has shed light on the correlation between MAFLD and neonatal outcomes. The study revealed that pregnant women with MAFLD were at a 2.82-fold higher risk of delivering LGA infants compared with their non-MAFLD counterparts.[66] In 2022, a subsequent and more extensive study involving 762,401 women revealed that women with MAFLD alone faced a 1.66-fold increase in the risk of preterm birth and a 1.35-fold increase in the risk of having infants with low birth weight compared with women without FLD. In contrast, those with only NAFLD did not show a significant increase in these risks.[42] Furthermore, Gross et al. conducted a prospective cohort assessment of the health outcomes in infants born to mothers diagnosed with NAFLD as well as those without the condition over a 2-year period. Their research suggests a potential independent link between NAFLD in expectant mothers and a higher likelihood of extremely preterm births and neonatal jaundice. However, their findings did not demonstrate a connection with additional negative outcomes in newborns.[79] Specifically, the study indicated that the risk of extremely preterm birth, occurring before 32 weeks of gestation, was 2.82 times higher for infants born to mothers with NAFLD compared with those born to mothers without the condition. Moreover, the risk of developing neonatal jaundice was 1.67 times greater in the NAFLD group.[79] These findings highlight the significant influence of maternal NAFLD on early neonatal health. However, the question as to whether MAFLD in pregnant women contributes to a higher incidence of jaundice in infants remains unanswered, underscoring the need for additional research in this area.

Treatment of MAFLD

MAFLD is a chronic liver disease that can progress to steatohepatitis, cirrhosis, and even HCC, and it is an indication for liver transplantation.[80–82] Recent studies have underscored the importance of early intervention; for example, research by Tushar Prabhakar in Delhi, India, showed that the risk of advanced liver fibrosis in MAFLD patients was threefold higher than that in non-patients.[83] Thus, the development of effective treatment strategies is particularly urgent.

Currently, lifestyle modifications are key in the management of MAFLD.[84,85] A cross-sectional study by Marjan Mokhtare indicated that adherence to the Mediterranean diet could reduce the severity of MAFLD.[86] Additionally, regular exercise, including both aerobic and resistance training, has been shown to significantly improve symptoms.[87,88] The American Association for the Study of Liver Diseases (AASLD) recommends that MAFLD patients engage in 150 min of aerobic exercise and resistance training per week. Moreover, it is suggested that individuals who are sedentary, such as those with desk-bound jobs, require a higher-quality diet.[89] In summary, a comprehensive lifestyle intervention that combines diet, nutrients, and exercise is crucial for the treatment of MAFLD.

In the current therapeutic landscape for MAFLD, management strategies often involve addressing the metabolic comorbidities associated with the condition, given the absence of approved medications specifically targeting MAFLD. The American Association of Clinical Endocrinology and the AASLD acknowledge the use of medications that modulate insulin sensitivity and metabolic regulation, which may indirectly benefit MAFLD patients.[90] Agents such as metformin, pioglitazone, and glucagon-like peptide-1 (GLP-1) receptor agonists, which are primarily used for type 2 diabetes management, are also being investigated for their potential to ameliorate the pathophysiological processes associated with MAFLD.[91–93] In addition to these, strategies aimed at modulating the gut microbiota also hold potential in managing MAFLD. Farnesoid X receptor agonists, Takeda G-Protein–Coupled Receptor 5 (TGR5) agonists, and probiotics are among the methods being investigated for their effects on liver health and the ability to prevent or treat MAFLD by influencing the gut–liver axis.[94]

For the pharmacological treatment of MAFLD in pregnant women, particular caution is required. While the Mediterranean diet is considered potentially beneficial in reducing offspring's cardiometabolic risk during pregnancy,[95] the options for pharmacotherapy are more limited. For example, the use of pioglitazone is restricted in pregnant women due to potential fetal toxicity.[96] Metformin, a common medication for type 2 diabetes, is generally considered safe during pregnancy, and the UK's National Institute for Health and Care Excellence recommends its use pre-pregnancy.[97] Therefore, metformin may be a viable option for the treatment of MAFLD during pregnancy, especially for those women who also have diabetes. However, more research is needed to support the effectiveness and safety of metformin for treating MAFLD during pregnancy.

In conclusion, the management of MAFLD should prioritize lifestyle interventions, supplemented by pharmacotherapy, and safe and effective treatment regimens should be developed for special populations, such as pregnant women. Future research needs to explore the optimal combination of these treatment modalities to improve the prognosis for patients with MAFLD and to provide more safe and effective treatment options for pregnant women.

Limitations

Current research on the relationship between MAFLD and pregnancy complications primarily relies on cross-sectional studies, which limits our ability to establish causality. Cross-sectional study designs capture data at a single point in time, making it difficult to determine the temporal sequence of events and understand the dynamic nature of MAFLD and its impact on pregnancy. Longitudinal studies are needed to better understand how MAFLD evolves over time and its causal relationship with pregnancy complications. Additionally, existing studies suffer from inadequate sample sizes, geographic distribution, and racial diversity, which restricts the generalizability and applicability of the findings. Future research should involve more extensive samples and diverse participants to provide more representative and comprehensive insights.

Conclusion

In summary, this review delineates the intricate interplay between MAFLD and adverse outcomes during pregnancy, signifying a pressing need for targeted research. The evidence underscores the association of MAFLD with increased risks of gestational hypertension, diabetes, and a propensity for cesarean deliveries, with obesity emerging as a pivotal risk factor. The roles of genetic and epigenetic mechanisms in the pathogenesis of MAFLD and their impact on pregnancy-related complications remain to be fully elucidated. Additionally, the gut microbiome's influence on MAFLD progression and maternal/infant health is a critical area for future exploration.

Current management of MAFLD prioritizes lifestyle interventions, with an emphasis on dietary and exercise regimens, while pharmacotherapeutic approaches, particularly in pregnant women, are navigated with prudence. Future research should aim to develop and rigorously validate therapeutic strategies that are both safe and effective for managing MAFLD during pregnancy, with the potential to improve outcomes for mothers and their offspring.

Declarations

Ethics approval and consent to participate

None.

Consent for publication
None.

Author contributions
Yang Zhang: Conceptualization; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Yifan Bu: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Rui Zhao: Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.

Cheng Han: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Availability of data and materials
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