Pregnancy and Metabolic-associated Fatty Liver Disease: A Clinical Update

Sherouk Fouda1, Madhu Mathew Vennikandam2, Joseph M. Pappachan3,4,5* and Cornelius J. Fernandez6

1School of Health and Biomedical Sciences, RMIT University, Melbourne, VIC, Australia; 2Department of Gastroenterology and Hepatology, Sparrow Hospital, Michigan State University College of Human Medicine, Lansing, MI, USA; 3Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston, UK; 4Faculty of Science, Manchester Metropolitan University, Manchester, UK; 5Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; 6Department of Endocrinology & Metabolism, Pilgrim Hospital, Boston, UK

Received: 2 February 2022 | Revised: 15 March 2022 | Accepted: 26 April 2022 | Published: 26 May 2022

Abstract

The intricate relationship between metabolic-associated fatty liver disease (MAFLD) and maternal complications has rapidly become a significant health threat in pregnant women. The presence of MAFLD in pregnancy increases the maternal risk of metabolic complications and comorbidities for both mother and baby. The preexistence or development of MAFLD in pregnancy is a complex multifactorial disorder that can lead to further complications for mother and baby. Therefore, as pregnant women are severely underrepresented in clinical research, there is a great need for a fair inclusion of this group in clinical trials. This review aims to explore the effects of MAFLD during pregnancy in the context of maternal complications and outcomes and explore the effects of pregnancy on the development and progression of MAFLD within the context of maternal obesity, altered metabolic profiles, gestational diabetes and altered hormonal profiles. We also addressed potential implications for the presence of MAFLD during pregnancy and its management in the clinical setting.

Citation of this article: Fouda S, Vennikandam MM, Pappachan JM, Fernandez CJ. Pregnancy and Metabolic-associated Fatty Liver Disease: A Clinical Update. J Clin Transl Hepatol 2022;10(5):947–954. doi: 10.14218/JCTH.2022.00052.

Introduction

Metabolic-associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is the most common chronic disease affecting the liver in the US and probably in most countries across the globe. It is a metabolic disorder closely linked with abdominal adiposity, obesity, type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular disease (CVD) and affects nearly one-quarter of the global population leading to high morbidity and mortality.1,2 In recent years, nonalcoholic steatohepatitis (NASH) has become the most common indication for liver transplants in women.3,4 With the rising prevalence of obesity globally, the prevalence of MAFLD is expected to increase exponentially in the coming years. Emerging data suggests that the prevalence of MAFLD is becoming alarmingly high among children and young adults.3–7 MAFLD prevalence in pregnancy has almost tripled over the past 10 years.8,9 It is estimated that there is a 10% prevalence of MAFLD among women of childbearing age (20–40 years old).10 A recent large cohort study from South Korea showed that 18.4% of pregnant women had MAFLD in the first trimester of pregnancy.11 Higher disease prevalence during pregnancy is likely in the Western world owing to the higher proportion of obese individuals in these geographical areas. The reported prevalence of MAFLD using liver ultrasound was between 17% and 46%, depending on the population and demographics.10,12,13

Due to the body’s biotransformation experienced during pregnancy, pregnancy-related liver diseases are trimester-specific in occurrence. During pregnancy, women can develop primary liver diseases such as the idiopathic obstruction to the hepatobiliary tree causing intrahepatic cholestasis characterized by high conjugated bilirubin levels and high levels of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The presence of MAFLD in pregnancy is implicated in the development of various maternal health issues, including maternal hypertensive complications, postpartum hemorrhage, and premature birth.8 The risk factors contributing to MAFLD development and progression in pregnancy are less clear. The effect of pregnancy on MAFLD development and progression is of great interest as this will identify risk factors obstetricians can use to screen this underrepresented group. This increases the relevance of understanding the impact of MAFLD in pregnancy and vice-versa. In this review, we discuss the impact of MAFLD on maternal and fetal outcomes in pregnancy with the recommendations of obstetric management among women with MAFLD in pregnancy. We also briefly outline the potential impact...
of maternal MAFLD on the offspring’s lifelong metabolic health.

Pathophysiology of MAFLD in pregnancy

MAFLD is associated with insulin resistance and various components of the metabolic syndrome, including obesity, T2DM, hypertension, hyperlipidemia, with T2DM independently causing an increased risk of MAFLD by 2-fold. As MAFLD shares many of the risk factors for metabolic syndrome, MAFLD is considered the hepatic manifestation of metabolic syndrome. In response to overnutrition (i.e. a high fat diet) and obesity, there is an increase of free fatty acid uptake and lipogenesis with decreased fatty acid oxidation and very low-density lipoprotein (VLDL) secretion, leading to ectopic triglyceride deposition in the liver. This hepatic steatosis leads to lipotoxicity-mediated oxidative stress and/or endoplasmic reticulum stress leading to hepatocyte injury (apoptosis), inflammation, and fibrosis. As hepatic lipid deposition and hepatic insulin resistance often precede the skeletal muscle lipid deposition, macrophage-driven inflammation, extrahepatic insulin resistance, and hyperglycemia, MAFLD often precedes the other metabolic components of metabolic syndrome. Studies have shown that intrahepatic triglyceride content correlates more with obesity-related metabolic dysfunction than visceral obesity.

Altered secretion of hepatokines (hormone-like proteins secreted by the hepatocytes similar to adipokines secreted by the adipose tissue) including fetuin-A (FETUA), fetuin-B (FETUB), angiopoietin-like proteins (ANGPTLs), fibroblast growth factor 1 (FGF21), selenoprotein P, leukocyte elastin, cell-derived chemotaxin 2 (LECT2), hepsacin, follistatin, retinoic acid binding protein 4 (RBP4), SPARC-related modular calcium-binding protein 1 (SMOC1), and growth differentiation factor 15 (GDF15) has been implicated in the development and progression of MAFLD and insulin resistance. Except for FGF21, all hepatokines impair insulin signaling. Fetuin-A and LECT2 upregulate pro-inflammatory cytokine production to promote the macrophage-driven inflammation. Fetuins, LECT2, and hepsasin upregulate the lipogenic genes to enhance hepatic steatosis. On the other hand, FGF21 suppresses hepatic steatosis.

There is a bidirectional association between gestational diabetes mellitus (GDM) and MAFLD in women. Owning to the growing number of pregnancies in overweight and obese women, an increase in GDM pregnancies is a real concern. Additionally, there is an association between MAFLD and hypertensive outcomes like gestational hypertension and preeclampsia, independent of high body mass index (BMI). The pathogenesis of preeclampsia includes the release of pro-inflammatory cytokines and systemic inflammation caused by obesity, insulin resistance and hyperinsulinemia. The insulin resistance associated with MAFLD also results in activation of the renin-angiotensin-aldosterone system, with the development of hypertension in the mother as an important consequence.

Children exposed in utero to maternal MAFLD during pregnancy demonstrated a higher risk of early obesity and pediatric MAFLD, especially with histologically confirmed severe liver damage. Though the heritability of MAFLD from mother to offspring may be explainable through the association between genetic variants such as patatin-like phospholipase domain-containing protein 3 (PNPLA3) and susceptibility for hepatic steatosis, a more possible reason for the development of MAFLD in the offspring of mothers with peripartum MAFLD, would be its association with GDM and other metabolic risk factors. Other risk factors associated with pediatric MAFLD include maternal obesity, gestational diabetes, metabolic syndrome in pregnancy, and low birth weight. Thus, MAFLD and GDM exhibit transgenerational effects, whereby the metabolic dysfunction is passed from one generation to the next, creating a vicious cycle. Evidence from human and animal studies showed that metabolic syndrome originates from insults in utero, such as anoxia and overnutrition. Maternal hyperglycemia in utero can also predispose to metabolic dysfunction and obesity in the offspring. Maternal hyperglycemia with transplacental transfer of excess maternal glucose leads to the development of fetal hyperglycemia, fetal hyperinsulinemia, excessive fetal growth, hepatic steatosis, and a lifelong predisposition to metabolic dysfunction in the offspring. Maternal obesity causes preferential differentiation of mesenchymal umbilical cord cells into adipocytes resulting in neonatal adiposity within 72 hours of birth.

Transplacental transfer of excess maternal fatty acids cause accumulation of fetal ectopic lipids and predispose to obesity and insulin resistance, as per the multi-hit hypothesis of pediatric MAFLD. Intrauterine growth retardation can lead to pediatric obesity, MAFLD and metabolic syndrome, as per the thrifty-phenotype hypothesis of pediatric MAFLD. Maternal insulin resistance and hyperinsulinemia are associated with impaired placental blood flow, decreased fetal oxygen delivery, fetal anoxia, oxidative stress, generation of pro-inflammatory cytokines and resultant inflammation. A maternal high fat diet can cause intrauterine inflammation and steatogenesis. A recent single nucleotide polymorphism (SNP) 1 (SCD1) gene expression in neonatal hepatocytes resulting in abnormal hepatic lipid metabolism in the offspring and MAFLD. SCD1 is normally responsible for converting saturated fatty acids to monounsaturated fatty acids in the liver. Animal experiments observed that maternal exposure to a high-fat diet during pregnancy and lactation could have lasting effects in increasing insulin resistance, associated with hepatic inflammation even in offspring with normal weight. Animal experiments also showed that maternal exposure to a high-fat diet is associated with a disruption in the methionine cycle and one-carbon metabolism in the offspring livers. These result in DNA hypermethylation and L-carnitine depletion, associated with deactivation of AMP-activated protein kinase (AMPK) signaling and reduction in the expression of peroxisome proliferator-activated receptor alpha (PPAR-α) and genes for fatty acid oxidation, which in turn alters the lipid homeostasis in the offspring.

Effects of pregnancy on development and progression of maternal MAFLD

Physiological stress in pregnancy is characterized by increased visceral adiposity accompanied by an increase in hepatic lipid accumulation, amplifying the risk of metabolic complications such as GDM and hepatic insulin resistance. In fact, women with prior GDM are at a two-fold higher risk of developing MAFLD compared with women without a history of GDM, independent of BMI. Several other studies demonstrated that women with GDM are at a higher risk of developing MAFLD later in life than women without GDM. Studies also clearly show that the rise of fatty liver disease in pregnancy is largely driven by the obese metabolic phenotype. Additionally, the prevalence of maternal obesity and a maternal diet high in sugar intake is increasing globally, predisposing pregnant women to develop MAFLD. While no human studies have directly looked at the association between maternal energy intake and maternal MAFLD development, low birth weight, high maternal BMI, maternal DM, and gestational weight gain can play a role in increased hepatic fat and MAFLD in pregnant women. Experimental studies have shown that ma-
Fig. 1. The effects of pregnancy on MAFLD development. Evidence suggests that factors such as maternal adiposity, pre-existing obesity, hypercholesterolemia, gestational diabetes, pre-existing metabolic syndrome, and genetic predisposition in pregnant women may promote increased inflammatory responses, hormonal dysregulation, increased lipotoxicity and dyslipidemia, epigenetic alterations and insulin resistance. In utero exposure to these factors may increase the risk of childhood MAFLD through placental transfer. Also, such factors may affect adipogenesis and disrupt metabolism in the mother leading to maternal MAFLD development. Lastly, exposure to these factors may lead to MAFLD development in premenopausal women. MAFLD, Metabolic-associated fatty liver disease.

Effects of maternal MAFLD on pregnancy outcomes

Most patients with MAFLD are clinically asymptomatic. Some may develop elevated liver enzymes, which are discovered incidentally—due to steatohepatitis. The elevation of liver enzymes in pregnant patients can be a challenge for the consulting clinician. There have been several studies suggesting negative pregnancy outcomes with comorbid MAFLD. A systematic review and meta-analysis observed a strong association between MAFLD and adverse maternal and fetal outcomes, including hyperglycemia, pregnancy-associated hypertension, cesarean section, and preterm delivery. Prior studies on pregnancy and MAFLD have shown that the presence of MAFLD has been associated with maternal hyperglycemia and gestational diabetes. MAFLD in pregnancy is an independent risk factor for insulin-requiring GDM. Patients with MAFLD diagnosed during the first trimester of pregnancy had a higher risk of impaired fasting glucose, impaired glucose tolerance, and GDM in the mid-pregnancy, and the above risk was proportionate to the severity of steatosis. The presence of low adiponectin and high selenoprotein-P levels were found to be related to the severity of MAFLD detected biochemically and via ultrasound, which were also found to be independent predictors.
Fouda S. et al: Pregnancy and MAFLD: a clinical update

- Pregnancy with or without associated maternal obesity \rightarrow\text{ insulin resistance (IR)}
- IR \rightarrow\text{ hyperinsulinemia} \rightarrow\text{ hyperglycemia} \rightarrow\text{ gestational diabetes mellitus (GDM)}
- IR \rightarrow\text{ proinflammatory cytokine} \rightarrow\text{ chronic low grade inflammation} \rightarrow\text{ hypertension}
- IR \rightarrow\text{ activation of RAAS} \rightarrow\text{ hypertension}

- Increased FFA uptake and lipogenesis associated decreased β oxidation and VLDL secretion \rightarrow\text{ Ecotoxic TG deposition}
- Ecotoxic hepatic lipid \rightarrow\text{ oxidative and ER stress} \rightarrow\text{ lipotoxicity} \rightarrow\text{ hepatocyte injury} \rightarrow\text{ apoptosis, inflammation and fibrosis}
- Ecotoxic hepatic lipid \rightarrow\text{ altered hepatokine secretion} \rightarrow\text{ worsening IR}

- Maternal high fat diet combined with physical inactivity \rightarrow\text{ insulin resistance} \rightarrow\text{ intrauterine inflammation}

- Maternal adiposity and obesity
- Transplacental transfer of glucose
- Transplacental transfer of FFA
- Impaired placental blood flow
- Placental exposure to excess nutrients
- Upregulation of SCD1 expression in neonatal hepatocytes \rightarrow\text{ abnormal hepatic lipid metabolism in offspring} \rightarrow\text{ MAFLD with hepatic inflammation and alteration lipid homeostasis}

- Fetal side
- Differentiation of fetal umbilical mesenchymal stem cells into adipocytes \rightarrow\text{ neonatal adiposity}
- Fetal hyperglycemia and hyperinsulinemia \rightarrow excessive fetal growth-hepatic steatosis \rightarrow serving as one of the multiple "first hits" \rightarrow lifelong predisposition to MAFLD, obesity, IR, and metabolic dysfunction in the offspring

- Fetal ectopic hepatic lipid deposition \rightarrow non-alcoholic fatty liver disease in offspring
- Fetal ectopic lipid deposition \rightarrow serving as one of the multiple "first hits" \rightarrow lifelong predisposition to obesity and metabolic dysfunction in offspring
- Decreased fetal oxygen delivery \rightarrow anoxia \rightarrow oxidative stress \rightarrow proinflammatory cytokines \rightarrow inflammation \rightarrow IR & metabolic dysfunction

- Placenta
- Maternal side

Effects of maternal MAFLD on offspring

The first published evaluation of breastfeeding on MAFLD based on the CARDIA cohort\textsuperscript{26,75} showed an inverse correlation between self-reported lactation duration and maternal MAFLD rates at 8.3\% for 0 to 1 month, 7.7\% for 1 to 6 months, and 4.2\% for more than 6 months. It also showed that women with longer lactation duration had a lower BMI, HOMA-IR, triglycerides, and waist circumference.\textsuperscript{75} Analysis of the data from a large prospective study from Bristol, UK (the Avon Longitudinal Study of Parents and Children) showed that there is no strong association between longer breastfeeding duration and protection against offspring developing MAFLD.\textsuperscript{76} This recent result contrasts the previous observation that ≥6 months of exclusive breastfeeding was associated with lower odds of MAFLD outcomes in offspring, lower gamma-glutamyl transpeptidase (GGT), and triglyceride levels at 17 years.\textsuperscript{77} However, both these studies observed that higher pre-pregnancy BMI is associated with greater odds of MAFLD outcomes in offspring.

Maternal MAFLD was also found to be associated with higher risk for future development of metabolic diseases including MAFLD and T2DM in the offspring during adolescence and adulthood. Observations from the large long term Western Australian Raine cohort study point towards strong association between several maternal characteristics like obesity, gestational weight gain and MAFLD with development of various cardiometabolic disorders in the offspring including MAFLD during adolescence and adult life.\textsuperscript{76,78} These results reinforce the importance of rigorous lifestyle interventions to prevent MAFLD in such children born to mothers with the disease. The effects of pregnancy-related metabolic dysregulation and maternal MAFLD on the fetus is demonstrated in Figure 2.

Investigations for pregnancy-related MAFLD

Newly diagnosed liver abnormalities in pregnancy necessitate diagnostic evaluation informed by gestational age, patient’s medical history and the predicted physiologic changes of pregnancy. Pharmacological agents that would be ap-
proved for MAFLD will most likely not be suitable in pregnant women with MAFLD. In fact, MAFLD can develop de novo during pregnancy or can exist prior to pregnancy. There are no specific guidelines or diagnostic algorithms to screen and identify MAFLD and its complications in pregnancy. Furthermore, there is an apparent lack of known mechanisms in the literature that identifies specific pathways for the de novo development of MAFLD during pregnancy, and most of the literature depicts the development of MAFLD prior to the pregnancy. While liver biopsy remains the gold standard to confirm MAFLD diagnosis, a screening algorithm needs to be based on non-invasive testing. Assessment of BMI and fatty liver index (FLI) would be beneficial.79 Biomarkers like adiponectin and selenoprotein P are promising in formulating a screening algorithm. However, the cost-effectiveness needs to be considered, and there is a need for large prospective studies to understand the utility of the biomarkers and FLI. Although ultrasound (US) has limited sensitivity and specificity for diagnosing fatty liver,80 it can be beneficial as an initial screening imaging modality due to its easy availability and safety. The Controlled Attenuation Parameter (CAP) during transient liver elastography (TLE) using a Fi- broScan is a well-studied modality to detect fatty liver in non-pregnant patients. The test can detect milder subclinical stages of fatty liver disease and assess the degree of fibrosis; however, the data on this modality on pregnant patients is sparse. FLI is a non-invasive test and a powerful diagnostic modality that can estimate MAFLD with reasonably high accuracy which has been validated in multiple model systems.79 Clinical and biochemical parameters used to derive FLI were waist circumference, BMI, triglyceride, and GGT levels. Compared with control women, women with abnormal FLI were also at elevated risk for having GDM. In pregnant women, FLI is a poor marker for MAFLD particularly after the first trimester and therefore, other non-invasive steatosis indices may be better used in pregnant women with mild or moderate MAFLD.

Management of MAFLD in pregnancy

The management of MAFLD is a multimodal approach. Management should identify the population at risk and prevent complications by controlling hyperglycemia, preventing GDM, avoiding excessive weight gain during pregnancy, and encouraging lactation for over 6 months post pregnancy, which can help reduce the burden and negative implications of MAFLD among mother and offspring. An early assessment of MAFLD is essential in maternal counselling. There is no single medication that is known to improve MAFLD in pregnancy. However, treatment should be aimed at managing obesity prior to pregnancy and managing pregnancy-related complications like GDM and gestational hypertension. The AASLD 2018 guidelines for the diagnosis and management of MAFLD (not for pregnancy) recommend that lifestyle interventions should target a weight loss of 7–10% of total body weight; should achieve a daily caloric deficit of 500–1,000 Calories, and moderate-intensity exercise, preferably in a structured weight loss program.81 Lifestyle and weight management in the postpartum period are important to reverse the effects of MAFLD and prevent complications in subsequent pregnancies. Breastfeeding has been known to be associated with lowered glucose and triglycerides and improved insulin sensitivity.82,83

Nutritional interventions

A systematic review and meta-analysis of eight randomized controlled trials observed that dietary interventions in the form of Mediterranean and hypocaloric dietary interventions with food items high in unsaturated fatty acids improve intrahepatic lipid content and transaminase levels in patients with MAFLD.84 Animal experiments in pregnant mice observed that dietary interventions initiated sufficiently early before pregnancy and continued during pregnancy and lactation would reduce the risk of developing MAFLD even after exposure to a maternal high fat diet prior to pregnancy.85 Although similar results may also be expected in human beings, nutritional interventions during pregnancy should balance the associated risks of malnutrition in the mother and offspring as there is only sparse evidence for these types of interventions based on good quality clinical studies.

Physical activity interventions

A systematic review and meta-analysis of 10 randomized controlled trials observed that exercise without significant weight loss has a beneficial effect on MAFLD as it is associated with a significant reduction in the intrahepatic lipid content, transaminase levels, low-density lipoprotein cholesterol levels, and triglycerides levels.86 In another systematic review, aerobic and resistance exercises reduced hepatic steatosis in MAFLD patients when done for 40–45 minutes per session 3 times per week for 12 weeks.87 Resistance exercise improved the MAFLD with less energy consumption, indicating that resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate aerobic exercises.

In animal experiments, exercise by the pregnant mother offers protection against MAFLD in the offspring via hepatic metabolic programming early in life, which is associated with a reduction in hepatic lipogenesis and an increase in hepatic β-oxidation.88 This metabolic programming is mediated by the activation of hepatic AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor alpha (PPARα) and PPAR-γ-cocoylinator-1 alpha (PGC1α).89 Again, extrapolation of these promising translational study results from animal models to human beings must be done with caution, considering the potential for complications during the early phase of pregnancy, such as miscarriage and placental abruption during the later stage. However, moderate exercise during pregnancy has been historically associated with better maternal and fetal outcomes and, therefore, would be expected to benefit even patients with MAFLD.

Therapeutic interventions

There are currently no approved drugs to treat MAFLD or NASH. However, multiple drugs are in phase 2 & 3 clinical trials for development. The AASLD 2018 guidelines for the diagnosis and management of MAFLD (not for pregnancy) recommends that in NASH and compensated cirrhosis patients with cardiovascular indications, statins can be safely used.81 Vitamin E 800 IU daily can be considered in nondiabetic patients with biopsy-proved NASH without cirrhosis, and Pioglitazone 30 mg daily can be considered in patients with and without T2DM with biopsy-proved NASH. Lanifibranor, a pan-PPAR agonist, in phase 2 trials is a promising new treatment indicated for NASH patients with fibrosis known to improve fibrosis stage with/without NASH resolution.90 Another promising treatment for NASH in phase 3 trials is obeticholic acid, a farnesoid X receptor agonist that has shown clinically significant improvements in histological disease activity.91 However, none of these drugs are deemed safe in pregnancy with MAFLD. Hence, lifestyle in-
terventions with diet and exercise remain the cornerstone in the management. A recent study demonstrated that metformin ameliorates the effects of high-fat induced hepatic steatosis in maternal rats and fetal liver cell apoptosis and intestinal inflammation. Although metformin is safe during pregnancy, there is no human data for the routine use of this promising agent in pregnant women with MAFLD.

Conclusion

Pregnancy-related liver disorders exhibit a trimester-specific occurrence. Several studies thus far have shown that MAFLD is a major risk factor for the development of GDM, and it is an independent risk factor for GDM, regardless of the status of metabolic syndrome. The timely diagnosis of clinical manifestations, including abnormal liver function tests, is critical for prognosis and therapeutic decisions to minimize the implications for both the mother and child and to determine maternal and fetal outcomes in severe liver disease cases. Therefore, early identification of women with MAFLD is important and more intensive screening and pre-disease cases. Therefore, early identification of women with MAFLD is associated with adverse maternal and perinatal outcomes. J Hepatol 2020;73(3):516–522. doi:10.1016/j.jhep.2020.03.049. PMID:32531415.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study conception and design (JMP and CJF), analysis and interpretation of data (SF, MMV and CJF), drafting of the manuscript (SF and MMV), administrative, technical, or material support, and study supervision (SF, CJF and JMP).

References

[1] Younossi Z, Tacke F, Arrese C, Todo T, Kim IK, Alkhouri N, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology 2019;69(6):2672–2682. doi:10.1002/hep.30251. PMID:30179269.
[2] Ou W, Ma T, Cai J, Zhang X, Zhang P, She Z, et al. Liver Fibrosis and MAFLD: From Molecular Aspects to Novel Pharmacological Strategies. Front Med (Lausanne) 2021;8:761538. doi:10.3389/fmed.2021.761538. PMID:34746195.
[3] Nourreddin M, Vipani A, Breesee C, Todo T, Kim IK, Alkhouri N, et al. NASH Leading Cause of Liver Transplant in Women: Understanding the Risk for Liver Transplant and Ethnic and Gender Variances. Am J Gastroenterol 2018;113(11):1649–1659. doi:10.1038/s41395-018-0088-6. PMID:29880964.
[4] Doycheva I, Issa D, Watt KD, Lopez R, Rifaï G, Alkhouri N. Nonalcoholic Steatohepatitis is the Most Rapidly Increasing Indicator for Liver Transplantation in Young Adults in the United States. J Clin Gastroenterol 2018;52(4):339–346. doi:10.1097/MCG.0000000000002925. PMID:29861576.
[5] Ajmera VH, Gunderson EP, VanWagner LB, Lewis CE, Carr JJ, Terrault NA. Gestational Diabetes Mellitus Is Strongly Associated With Non-Alcoholic Fatty Liver Disease. J Pediatr 2019;211:72–77.e4. doi:10.1016/j.jpeds.2019.04.018, PMID:30903256.
[6] Lopez-Jaramillo P, Barajas J, Rueda-Quijano SM, Lopez-Lopez C, Felix C. Nonalcoholic fatty liver: disease as a manifestation of the metabolic syndrome. Clev Clin J Med 2008;75(10):721–728. doi:10.3949/ccjm.2008.0925. PMID:18939388.
[7] Ajmera VH, Gunderson EP, VanWagner LB, Lewis CE, Carr JJ, Terrault NA. Non-Alcoholic Fatty Liver Disease Is Prevalent in Women With Prior Nonalcoholic Fatty Liver Disease. Gastroenterology 2017;152(5):1174–1179. doi:10.1053/j.gastro.2017.04.016. PMID:28113482.
[8] Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling or consequence of type 2 diabetes? Liver Int 2016;36(11):1563–1579. doi:10.1111/lci.13185. PMID:27276071.
[9] Lee C, Kim J, Jung Y. Potential Therapeutic Application of Estrogen in Gender Disparity of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis. Cells 2019;8(10):E1259. doi:10.3390/cells8101259. PMID:31691203.
[10] Kim TH, Hong DG, Yang YM. Hepatokines and Non-Alcoholic Fatty Liver Disease: Linking Liver Pathophysiology to Metabolism. Biomedicines 2021;9(12):1903. doi:10.3390/biomedicines9121903. PMID:34944728.
[11] Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked to metabolic complications of obesity. Proc Natl Acad Sci U S A 2009;106(36):15430–15435. doi:10.1073/pnas.0904494106. PMID:19706383.
[12] Targar纳 G, Byrne CD. Clinical Review: Nonalcoholic fatty liver disease: a novel cardiothabolic risk factor for type 2 diabetes and its complications. J Clin Endocrinol Metab 2013;98(2):483–495. doi:10.1210/jc.2012-3093. PMID:23293330.
[13] Ajmera VH, Gunderson EP, VanWagner LB, Lewis CE, Carr JJ, Terrault NA. Gestational Diabetes Mellitus Is Strongly Associated With Non-Alcoholic Fatty Liver Disease. Am J Gastroenterol 2016;111(5):608–614. doi:10.1038/ajg.2015.279. PMID:27027996.
[14] Foghsgaard S, Andresen C, Veldtroe I, Andersson ES, Bahne E, Strandberg C, et al. Nonalcoholic Fatty Liver Disease Is Prevalent in Women With Gestational Diabetes Mellitus and Independently Associated With Insulin Resistance and Waist Circumference. Diabetes Care 2017;40(1):73–84. doi:10.2337/dc16-1017. PMID:27810989.
[15] Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2018;9:1838. doi:10.3389/fphys.2018.01838. PMID:30618843.
[16] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic predisposition, programing during fetal life, family conditions, and post-natal diet in the development of Pediatric Fatty Liver Disease. J Pediatr. 2019;211:72–77.e7. doi:10.1016/j.jpeds.2019.04.018. PMID:31128866.
[17] Lopez-Jaramillo P, Barajas J, Rueda-Quijano SM, Lopez-Lopez C, Felix C. Obesity and Preeclampsia: Common Pathophysiological Mechanisms. Front Physiol 2019;8:1083. doi:10.3389/fphys.2018.01083. PMID:30618843.
[18] Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2012;17(5):330–341. doi:10.1177/1381612812450094. PMID:22814999.
[19] Mosca A, De Cosmi P, Parazzini F, Raponi M, Alisi A, Agostoni C, et al. The Role of Genetic Predisposition, Programming During Fetal Life, Family Conditions, and Post-natal Diet in the Development of Pediatric Fatty Liver Disease. J Pediatr. 2011;157:72–77.e4. doi:10.1016/j.jpeds.2011.04.018. PMID:22814999.
[20] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in the PPAR3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008;40(12):1461–1465. doi:10.1038/ng.257. PMID:18820647.
[21] Dongiovanni P, Anstee QM, Valentí L. Genetic predisposition in NAFLD and NASH: impact on severity of liver disease and response to treatment. Curr Pharm Des 2013;19(29):5219–5238. doi:10.2174/1381612811319999038. PMID:23394097.
[22] Hershman M, Me R, Kushner T. Implications of Nonalcoholic Fatty Liver Disease on Pregnancy and Maternal and Child Outcomes. Gastroenterol Hepatol (N Y) 2015;11(4):221–228. PMID:31435201.
Associations of maternal diet and nutritional status with offspring hepatic steatosis in the Avon longitudinal study of parents and children. BMC Nutr 2021;7(1):28. doi:10.1186/s40795-021-00433-3. PMID:34233762.

[53] Koylu M, Saltik A, Yüksel M, et al. Effect of abdominal obesity and lactation on the liver fat content in young adult rats. J Physiol Pharmacol 2013;15(1):356–357. doi:10.1002/ajp.2236735.

[54] Goldner D, Lavine JE. Nonalcoholic Fatty Liver Disease in Children: Unique Clinical Presentation and Outcome. Endocr Rev 2013;15(7):1967-1983. e1. doi:10.1210/en.2012-1877. PMID:23861176.

[55] Grossmann M, Wierman ME, Angus P, Handelsman DJ. Reproductive Endocrinology of Nonalcoholic Fatty Liver Disease. Endocr Rev 2019;40(2):417–453. doi:10.1210/en.2018-00158. PMID:30580887.

[56] Sarkar M, Djeboura M, Flemming JA. NAFLD Cirrhosis Is Rising Among Childbearing Women and Is the Most Common Cause of Cirrhosis in Pregnancy. Clin Gastroenterol Hepatol 2022;20(2):e315–e318. doi:10.1016/j.cgh.2021.01.022. PMID:33465683.

[57] Feingold KR, Brinton EA, Grunfeld C. The Effect of Endocrine Disorders on Lipids and Lipoproteins. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Heder WW, Dhakuria K, et al. (eds). Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000. PMID:28121116.

[58] Foulou CE, Trevilho LS, York B, Walker CL. Endocrine-disrupting chemicals and fatty liver disease. Nat Rev Endocrinol 2017;13(4):145–47. doi:10.1038/nrendo.2017.4. PMID:28524171.

[59] WD JD, Abdelmalek MF, Guy CD, Gill RM, Lavine JE, Yates K, et al. Patient Sex, Reproductive Status, and Synthetic Hormone Use Associate With Histologic Severity of Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol 2017;15(1):127–132.e1. doi:10.1016/j.cgh.2016.07.034. PMID:27523635.

[60] Flemming JA, Mullin M, Li J, Sarkar MA, Djeboura M, Velez MP, et al. Outcomes of Pregnant Women With Cirrhosis and Their Infants in a Population-Based Cohort Study. JAMA Intern Med 2020;756:1–7. doi:10.1001/jama.2018.5704. J-gastro.2020.07.052. PMID:32781083.

[61] Chaudhuri TK, Shukla S, Verma A, Hoyer MA, Singh J, Dufield K, et al. Model for end-stage liver disease score predicts outcome in cirrhotic patients during pregnancy. Clin Gastroenterol Hepatol 2011;9(8):694–699. doi:10.1016/j.cgh.2010.09.042. PMID:21704028.

[62] Sarkar M, Brady CW, Fleckenstein J, Forde KA, Khungar V, Moolten JP, et al. Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;73(1):318–365. doi:10.1002/hep.32496672.

[63] Wang J, Li Z, Lin L. Metabolic profiles in women with and without gestational diabetes mellitus. Medicine (Baltimore) 2019;98(16):e15320. doi:10.1097/MD.00000000000015320. PMID:31089886.

[64] Dyah AA, Rahadina R. Metabolic associated fatty liver disease and adverse maternal and fetal outcomes: a systematic review and meta-analysis. Clin Exp Obstet Gynecol 2021;48(3):305–311. doi:10.1515/cio.2019.0218. PMID:34714177.

[65] De Souza LR, Berger H, Retnakaran R, Vlachou PA, Maguire JL, Nathens AB, et al. Non-Alcoholic Fatty Liver Disease in Early Pregnancy Predicts Dysglycemia in Mid-Pregnancy: Prospective Study. Am J Obstet Gynecol 2016;111(5):665–670. doi:10.1016/j.ajog.2015.11.022. PMID:26977755.

[66] Mousa N, Abdel-Razek A, Shams M, Sheta T, Zakaria S, Shabanah W, et al. Impact of non-alcoholic fatty liver disease on pregnancy. Br J Ob- stet Gynaecol 2018;75(4):197–199. doi:10.1111/bjo.13948. PMID:29457404.

[67] You SY, Han K, Lee SH, Kim MK. Nonalcoholic fatty liver disease and the risk of insulin-requiring gestational diabetes. Diabetol Metab Syndr 2015;7:23. doi:10.1186/s13098-015-0176-4. PMID:26504274.

[68] Hegström H, Hörjé L, Ludvigsson JF, Böttm A, Ekborn A, Hultcrantz R, et al. Non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. J Gastroenterol Hepatol 2021;36(12):268–274. doi:10.1111/jgh.15287. PMID:31974650.

[69] Stannnes Kopp UM, Dahl-Jorgensen K, Stigmø H, Frost Andersen L, Næs S, Nystlad W. The associations between maternal pre-pregnancy body mass index or gestational weight change during pregnancy and body mass index of the child at 3 years of age. Int J Obes (Lond) 2012;36(10):1325–1331. doi:10.1038/ijo.2012.140. PMID:22992921.

[70] Sikov E, Homko CJ, Chen X, Reese EA, Boden G. Effect of insulin on fat metabolism during and after pregnancy. Diabetes 1999;48(4):834–838. doi:10.2337/diabetes.48.4.834. PMID:10102071.

[71] Odegaard JI, Ronaldo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, et al. Alternative M2 activation of Kupffer cells by PPARdelta amelio- rates obesity-induced insulin resistance. Cell Metab 2008;7(6):496–507. doi:10.1016/j.cmet.2008.04.003. PMID:18522831.

[72] Lin J, Jiang X, Dong M, Liu X, Shen Q, Huang Y, et al. Hepatokine Preg- nancy Zone Protein Governs the Diet-Induced Thermogenesis Through Activating Brown Adipose Tissue. Adv Sci (Weinh) 2021;8(21):e2101991. doi:10.1002/advs.202103024. doi:10.1002/advs.202103024. PMID:33801873.

[73] Herder WW, Dhatariya K, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. Cell Metab 2008;7(6):496–507. doi:10.1016/j.cmet.2008.04.003. PMID:18522831.

[74] Lin J, Jiang X, Dong M, Liu X, Shen Q, Huang Y, et al. Hepatokine Preg- nancy Zone Protein Governs the Diet-Induced Thermogenesis Through Activating Brown Adipose Tissue. Adv Sci (Weinh) 2021;8(21):e2101991. doi:10.1002/advs.202103024. doi:10.1002/advs.202103024. PMID:33801873.

[75] Ajmera VH, Terrault NA, VanWagner LB, Sarkar M, Lewis CE, Carr JJ, et al. One 2019;14(4):e0215326. doi:10.1371/journal.pone.0215326, PMID:30913204.
Fouda S. et al: Pregnancy and MAFLD: a clinical update

doi:10.1016/j.jhep.2018.09.013, PMID:30392752.

[76] Ayonrinde OT, Oddy WH, Adams LA, Mori TA, Beilin LJ, de Klerk N, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. J Hepatol 2017;67(3):568–576. doi:10.1016/j.jhep.2017.03.029, PMID:28619255.

[77] Fouda S. et al: Pregnancy and MAFLD: a clinical update

doi:10.1016/j.jhep.2018.09.013, PMID:30392752.

[78] Ayonrinde OT, Oddy WH, Adams LA, Mori TA, Beilin LJ, de Klerk N, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. J Hepatol 2017;67(3):568–576. doi:10.1016/j.jhep.2017.03.029, PMID:28619255.

[79] Abeysekera KW, Orr JG, Madley-Dowd P, Fernandes GS, Zuccolo L, Gordon FH, et al. Association of maternal pre-pregnancy BMI and breastfeeding with NAFLD in young adults: a parental negative control study. Lancet Reg Health Eur, 2021, 10:100206. doi:10.1016/j.lanepe.2021.100206, PMID:34806068.

[80] Dontje ML, Eastwood P, Straker L. Western Australian pregnancy cohort (Raine) Study: Generation 1. BMJ Open 2019;9(5):e026276. doi:10.1136/bmjopen-2018-026276, PMID:31138581.

[81] Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33. doi:10.1186/1471-230X-6-33, PMID:17081293.

[82] Bril F, Ortiz-Lopez C, Lomonaco R, Orsak B, Freckleton M, Chintapalli K, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. Liver Int 2015;35(9):2139–2146. doi:10.1111/liv.12840, PMID:31138581.

[83] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328–357. doi:10.1002/hep.29367, PMID:28714183.

[84] Houttu V, Csader S, Nieuwdorp M, Holleboom AG, Schwab U. Dietary Inter-ventions in Patients With Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Front Nutr 2021;8:716783. doi:10.3389/frnut.2021.716783, PMID:34368214.

[85] Zhou V, Peng H, Xu H, Li J, Golovko M, Cheng H, et al. Maternal diet intervention before pregnancy primes offspring lipid metabolism in liver. Lab Invest 2020;100(4):553–569. doi:10.1038/s41374-019-0344-4, PMID:31748681.

[86] Babu AF, Csader S, Lok J, Gómez-Gallego C, Hanihina K, El-Nezami H, et al. Positive Effects of Exercise Intervention without Weight Loss and Dietary Changes in NAFLD-Related Clinical Parameters: A Systematic Review and Meta-Analysis. Nutrients 2021;13(9):3135. doi:10.3390/nu13093135, PMID:34579012.

[87] Hashida R, Kawaguchi T, Bekki M, Osato M, Matsuse H, Nago T, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. J Hepatol 2017;66(1):142–152. doi:10.1016/j.jhep.2016.08.023, PMID:27639843.

[88] Bab-Gartz J, Kasper P, Großmann N, Breuer S, Janoschek R, Kretschmer T, et al. Maternal exercise conveys protection against NAFLD in the offspring via hepatic metabolic programming. Sci Rep 2020;10(1):15424. doi:10.1038/s41598-020-72022-6, PMID:32963289.

[89] Kasper P, Breuer S, Hoffmann T, Volken C, Janoschek R, Schmitz L, et al. Maternal Exercise Mediates Hepatic Metabolic Programming via Activation of AMPK-PGC1α Axis in the Offspring of Obese Mothers. Cells 2021;10(5):1247. doi:10.3390/cells10051247, PMID:34669390.

[90] Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021;385(17):1547–1558. doi:10.1056/NEJMoa2036205, PMID:34670042.

[91] Younossi ZM, Ratziu V, Loomba R, Mccarthy, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394(10215):2184–2196. doi:10.1016/S0140-6736(19)33041-7, PMID:31831363.

[92] Huang SW, Ou YC, Tang KS, Yu HR, Huang LT, Tain YL, et al. Mefenmetamol ameliorates maternal high-fat diet-induced maternal dysbiosis and fetal liver apoptosis. Lipids Health Dis 2021;20(1):100. doi:10.1186/s12944-021-01521-w, PMID:34496884.