



Review Article



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

Sherouk Fouda¹ , Madhu Mathew Vennikandam², Joseph M. Pappachan^{3,4,5*} 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. 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.^{5–7} 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 recommendation of obstetric management among women with MAFLD in pregnancy. We also briefly outline the potential impact

Keywords: Metabolic-associated fatty liver disease; Pregnancy; Maternal complications; Fatty liver.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; FGF21, fibroblast growth factor 21; FLI, fatty liver index; GDM, gestational diabetes mellitus; LECT2, leukocyte cell-derived chemotaxin 2; MAFLD, metabolic-associated liver disease; PPAR- α , peroxisome proliferator-activated receptor alpha; PPAR- γ , peroxisome proliferator-activated receptor gamma; SCD1, stearyl-CoA desaturase 1; T2DM, type-2 diabetes mellitus; TG, triglycerides.

*Correspondence to: Joseph M Pappachan, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT, UK. ORCID: <https://orcid.org/0000-0003-0886-5255>. Tel/Fax: +44-1-7725-22092, E-Mail: drpappachan@yahoo.co.in

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.¹⁴ As MAFLD shares many of the risk factors for metabolic syndrome, MAFLD is considered the hepatic manifestation of metabolic syndrome.¹⁵ 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.¹⁶ This hepatic steatosis leads to lipotoxicity-mediated oxidative stress and/or endoplasmic reticulum stress leading to hepatocyte injury (apoptosis), inflammation, and fibrosis.¹⁷ 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.¹⁸ Studies have shown that intrahepatic triglyceride content correlates more with obesity-related metabolic dysfunction than visceral obesity.¹⁹

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 21 (FGF21), selenoprotein P, leukocyte cell-derived chemotaxin 2 (LECT2), hepassocin, follistatin, retinol 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.²⁰ 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 hepassocin upregulate the lipogenic genes to enhance hepatic steatosis. On the other hand, FGF21 suppresses hepatic steatosis.¹⁸

There is a bidirectional association between gestational diabetes mellitus (GDM) and MAFLD in women.^{21,22} Owing 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.²³ The insulin resistance associated with MAFLD also results in activation of the renin-angiotensin-aldosterone system,²⁴ 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.²⁵ 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,^{26,27} 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.²⁸ Other risk factors associated with pediatric MAFLD include maternal obesity, gesta-

tional diabetes, metabolic syndrome in pregnancy, and low birth weight.²⁹ Thus, MAFLD and GDM exhibit transgenerational effects, whereby the metabolic dysfunction is passed from one generation to the next, creating a vicious cycle.²⁸ Evidence from human and animal studies showed that metabolic syndrome originates from insults *in utero*, such as anoxia and overnutrition.^{30,31} Exposure to hyperglycemia *in utero* can also predispose to metabolic dysfunction and obesity in the offspring.^{32–35} 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.³⁶

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.³⁷ Intrauterine growth retardation can lead to pediatric obesity, MAFLD and metabolic syndrome, as per the thrifty-phenotype hypothesis of pediatric MAFLD.³⁸ 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.³⁹ A maternal high fat diet can cause intrauterine inflammation and upregulation of stearoyl-CoA desaturase 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.⁴⁰ 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.⁴¹ 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.⁴²

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.^{14,22} 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.⁴³ Several other studies demonstrated that women with GDM are at a higher risk of developing MAFLD later in life than women without GDM.^{44–46} Studies also clearly show that the rise of fatty liver disease in pregnancy is largely driven by the obese metabolic phenotype.^{47,48} Additionally, the prevalence of maternal obesity and a maternal diet high in sugar intake is increasing globally, predisposing pregnant women to develop MAFLD.^{49,50} While no human studies have directly looked at the association between maternal energy rich diets and maternal MAFLD development, increased pre-pregnancy 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-

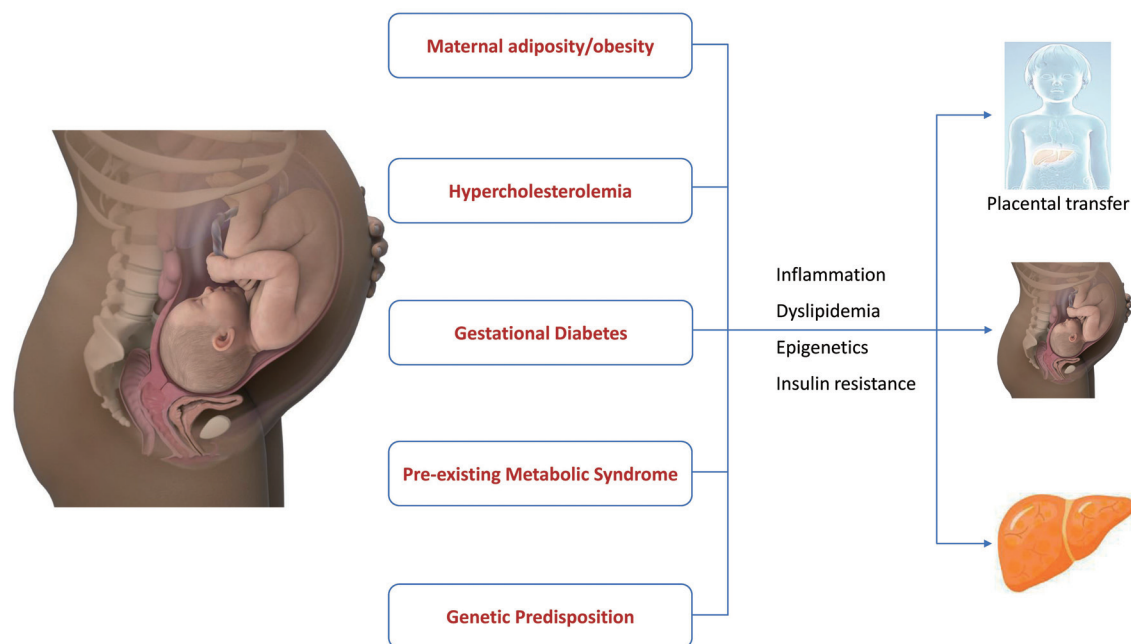


Fig. 1. The effects of pregnancy on MAFLD development. Evidence suggests that factors such as maternal adiposity, pre-existing obesity, hypercholesterolemia, gestational diabetes, pre-existing metabolic syndrome, and genetic predisposition in pregnant women may promote increased inflammatory responses, hormonal dysregulation, increased lipotoxicity and dyslipidemia, epigenetic alterations and insulin resistance. *In utero* exposure to these factors can 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.

teral diets high in sugar and fat can predispose even the offspring to MAFLD development.^{51–54} Figure 1 shows the effects of pregnancy on the development of MAFLD.

Sex hormone signaling contributes to the pathogenesis of MAFLD in a sexual dimorphic manner. Studies have shown that androgens promote hepatic steatosis, hepatic fibrosis, development of hepatocellular carcinoma, and dysglycemia in women, whereas estrogens inhibit all four.⁵⁵ Although MAFLD is less common in premenopausal women due to the protective effects of estrogen, women with dyslipidemia and/or obesity have an increased risk of developing fatty liver disease during pregnancy.⁵⁶ The dysregulation of cholesterol production in the liver is known to alter hormone production. As such, low cholesterol levels may lead to steroid hormone deficiency due to its critical role in hormone synthesis.⁵⁷ Steroid hormones such as sex hormones are largely affected by the levels of cholesterol and that of anabolic hormones such as insulin.^{57,58} Interestingly, studies found that premenopausal women with MAFLD who uses synthetic hormones show increased histologic severity of hepatocyte injury and inflammation in the liver, indicating that hormonal changes may increase hepatic metabolic stress.⁵⁹ The rise of cirrhosis in pregnancy is mainly associated with pregnancies with pre-existing MAFLD.⁵⁶ The maternal metabolic complications are mainly driven by a complex network of maternal metabolism risk factors leading to a high-risk pregnancy complicated by variceal hemorrhage ($\leq 50\%$) and hepatic decompensation ($\leq 25\%$).^{60,61} This highlights the importance of reproductive counselling in women with MAFLD as per the American Association for the Study of Liver Diseases (AASLD) guidance recommendations to ensure maternal metabolic complications are managed before conception and during pregnancy.⁶²

Clinical studies show that maternal lipid profiles increase dramatically during the second and third trimesters. It can be challenging to determine whether it is due to physiological or pathological changes. The strong association between ma-

ternal hyperlipidemia and GDM has been long documented.²² In fact, Wang *et al.* investigated the relationship between maternal lipid profile in the first trimester and GDM, and found that maternal age, pre-pregnancy BMI, and triglyceride/high density lipoprotein (TG/HDL) ratio were associated with an increased risk of GDM, which may be used as clinical markers to predict the risk of GDM.⁶³ As the GDM and maternal dyslipidemia increase the risk of metabolic diseases, pregnancy-complications, and postpartum-complications, it is proposed that the risk of MAFLD also increases.⁴⁴

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.⁶⁴

Prior studies on pregnancy and MAFLD have shown that the presence of MAFLD has been associated with maternal hyperglycemia and gestational diabetes.^{11,65,66} MAFLD in pregnancy is an independent risk factor for insulin-requiring GDM.⁶⁷ 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,^{11,65} and the above risk was proportionate to the severity of steatosis.¹¹ 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

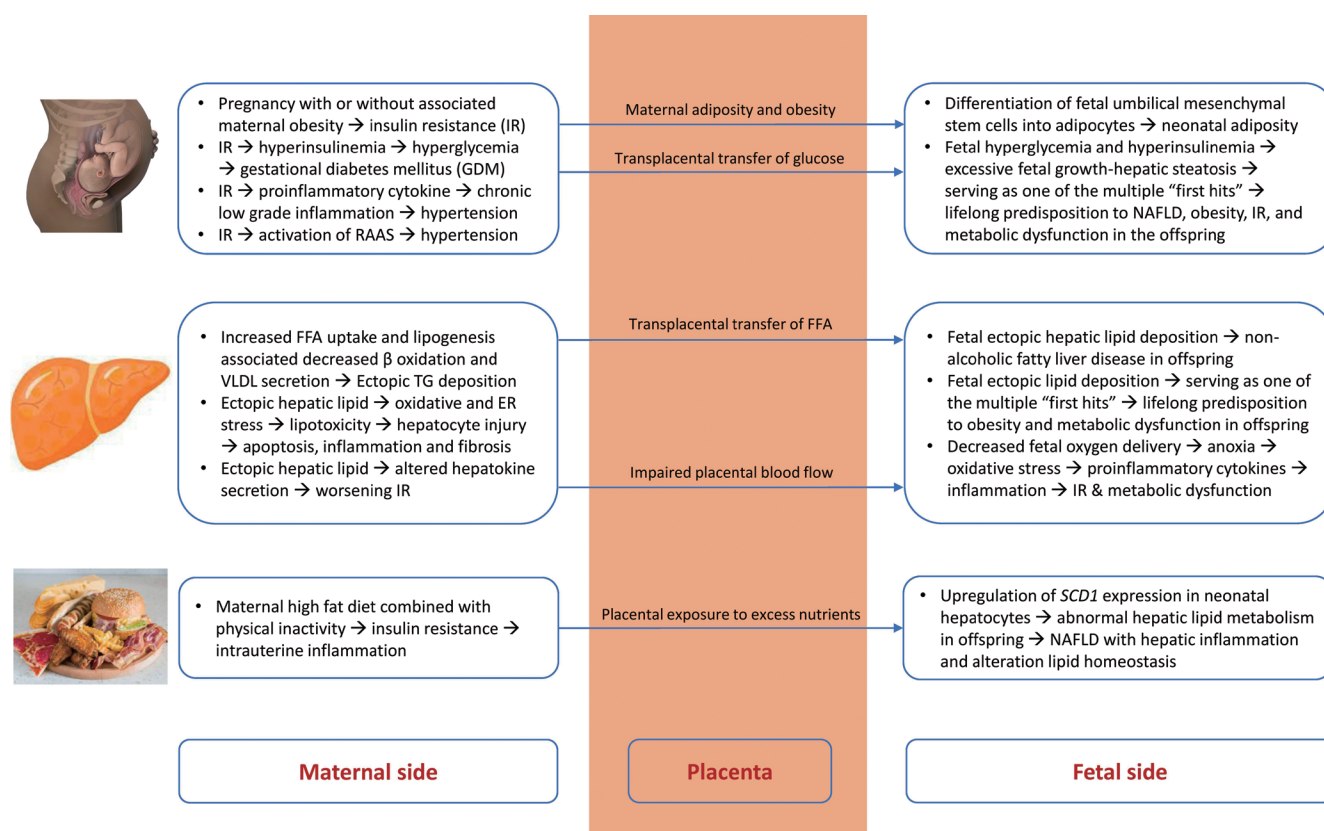


Fig. 2. Effects of metabolic dysregulation of pregnancy, MAFLD and maternal nutritional factors on the fetus. IR, insulin resistance; FFA, free fatty acid; VLDL, very low-density lipoprotein; TG, triglyceride; *SCD1*, stearoyl-CoA desaturase 1; MAFLD, Metabolic-associated fatty liver disease.

of GDM later in pregnancy.^{11,22} MAFLD in pregnancy is highly associated with increased maternal weight gain and obesity.^{68,69} The association between ‘maternal hyperglycemia and weight gain’ and increased pregnancy complications are well established in the literature.^{30,70}

Pregnancy itself is associated with an increase in insulin resistance as a physiologic response to ensure adequate carbohydrate supply to the growing fetus.⁷¹ Pregnancy with MAFLD is associated with a further rise in insulin resistance and increased risk of GDM due to the release of inflammatory cytokines such as tumor necrosis factor- α and interleukin- β from the fatty liver.⁷² A novel hepatokine, pregnancy zone protein (PZP), plays an important role in maintaining maternal energy homeostasis during pregnancy.⁷³ Research data from prior studies show a vulnerability to insulin resistance in pregnant patients with MAFLD in a pattern like that seen in GDM.^{21,22,43} Moreover, pregnant women with MAFLD have an increased risk of developing gestational hypertension and preeclampsia, independent of BMI ≥ 25 , age > 35 years, and hyperglycemia in pregnancy.⁷⁴

Effects of maternal MAFLD on offspring

The first published evaluation of breastfeeding on MAFLD based on the CARDIA cohort^{36,75} 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.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.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.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.^{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 FibroScan 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 offspring 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 (PPAR α) and PPAR- γ -coactivator-1 alpha (PGC1 α).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-

interventions with diet and exercise remain the cornerstones 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.⁹² 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 preventive strategies, especially in pregnancy and reproductive age group, is recommended. MAFLD in pregnancy is a high-risk condition, and it warrants pre-conception counselling and pregnancy care. There is still a lot to be known and to learn about the various intra- and extrauterine factors contributing to MAFLD in pregnancy. Due to the overlap of MAFLD with other metabolic risk factors, it is difficult to delineate the specific risk of MAFLD alone in pregnancy from retrospective studies, and we need more prospective studies to better understand the independent risk factors and impact of MAFLD in pregnancy and fetal outcomes.

Funding

None to declare.

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), critical revision of the manuscript for important intellectual content (SF, MMV, JMP and CJF), administrative, technical, or material support, and study supervision (SF, CJF and JMP).

References

- [1] Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, *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] Qu 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] Noureddin M, Vipani A, Bressee C, Todo T, Kim IK, Alkhouri N, *et al*. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications 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, Rifai G, Alkhouri N. Nonalcoholic Steatohepatitis is the Most Rapidly Increasing Indication for Liver Transplantation in Young Adults in the United States. *J Clin Gastroenterol* 2018;52(4):339–346. doi:10.1097/mcg.0000000000000925, PMID:28961576.
- [5] Li J, Le MH, Barakat MT, Cheung RC, Nguyen MH. The Changing Epidemiology of Liver Disease Among US Children and Adolescents From 1999 to 2016. *Am J Gastroenterol* 2021;116(10):2068–2078. doi:10.14309/ajg.0000000000001386, PMID:34328446.
- [6] Arshad T, Paik JM, Biswas R, Alqahtani SA, Henry L, Younossi ZM. Nonalcoholic Fatty Liver Disease Prevalence Trends Among Adolescents and Young Adults in the United States, 2007–2016. *Hepatol Commun* 2021;5(10):1676–1688. doi:10.1002/hep4.1760, PMID:34558817.
- [7] Paik JM, Kabbara K, Eberly KE, Younossi Y, Henry L, Younossi ZM. Global burden of NAFLD and chronic liver disease among adolescents and young adults. *Hepatology* 2022;75(5):1204–1217. doi:10.1002/hep.32228, PMID:34741554.
- [8] Sarkar M, Grab J, Dodge JL, Gunderson EP, Rubin J, Irani RA, *et al*. Non-alcoholic fatty liver disease in pregnancy 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.
- [9] Rajagopal S, Whetstone S, Sarkar M. Relevance of reproductive health to comprehensive hepatology care. *Lancet Gastroenterol Hepatol* 2021;6(4):260–262. doi:10.1016/S2468-1253(21)00055-8, PMID:33714364.
- [10] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;34(3):274–285. doi:10.1111/j.1365-2036.2011.04724.x, PMID:21623852.
- [11] Lee SM, Kwak SH, Koo JN, Oh JH, Kwon JE, Kim BJ, *et al*. Non-alcoholic fatty liver disease in the first trimester and subsequent development of gestational diabetes mellitus. *Diabetologia* 2019;62(2):238–248. doi:10.1007/s00125-018-4779-8, PMID:30470912.
- [12] Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. *Ann Gastroenterol* 2018;31(3):288–295. doi:10.20524/aog.2018.0240, PMID:29720854.
- [13] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64(1):73–84. doi:10.1002/hep.28431, PMID:26707365.
- [14] Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* 2014;59(3):1174–1197. doi:10.1002/hep.26717, PMID:24002776.
- [15] Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. *Cleve Clin J Med* 2008;75(10):721–728. doi:10.3949/ccjm.75.10.721, PMID:18939388.
- [16] Valenti L, Bugianesi E, Pajvani U, Targher G. Nonalcoholic fatty liver disease: cause or consequence of type 2 diabetes? *Liver Int* 2016;36(11):1563–1579. doi:10.1111/liv.13185, PMID:27276701.
- [17] 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:31619023.
- [18] 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.
- [19] Fabbri E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, *et al*. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A* 2009;106(36):15430–15435. doi:10.1073/pnas.0904944106, PMID:19706383.
- [20] Targher G, Byrne CD. Clinical Review: Nonalcoholic fatty liver disease: a novel cardiometabolic 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.
- [21] 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):658–664. doi:10.1038/ajg.2016.57, PMID:27002796.
- [22] Foghsgaard S, Andreassen C, Vedtofte L, Andersen ES, Bahne E, Strandberg C, *et al*. Nonalcoholic Fatty Liver Disease Is Prevalent in Women With Prior Gestational Diabetes Mellitus and Independently Associated With Insulin Resistance and Waist Circumference. *Diabetes Care* 2017;40(1):109–116. doi:10.2337/dc16-1017, PMID:27810989.
- [23] Lopez-Jaramillo P, Barajas J, Rueda-Quintero SM, Lopez-Lopez C, Felix C. Obesity and Preeclampsia: Common Pathophysiological Mechanisms. *Front Physiol* 2018;9:1838. doi:10.3389/fphys.2018.01838, PMID:30618843.
- [24] 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:10.1177/1358863x12450094, PMID:22814999.
- [25] Mosca A, De Cosmi V, 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* 2019;211:72–77.e4. doi:10.1016/j.jpeds.2019.04.018, PMID:31128886.
- [26] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, *et al*. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008;40(12):1461–1465. doi:10.1038/ng.257, PMID:18820647.
- [27] Dongiovanni P, Anstee QM, Valenti 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:10.2174/1381612811319990381, PMID:23394097.
- [28] Hershtman M, Mei R, Kushner T. Implications of Nonalcoholic Fatty Liver Disease on Pregnancy and Maternal and Child Outcomes. *Gastroenterol Hepatol (N Y)* 2019;15(4):221–228. PMID:31435201.

- [29] Mosca A, Panera N, Maggiore G, Alisi A. From pregnant women to infants: Non-alcoholic fatty liver disease is a poor inheritance. *J Hepatol* 2020; 73(6):1590–1592. doi:10.1016/j.jhep.2020.06.043, PMID:32958329.
- [30] Dabelea D, Crume T. Maternal environment and the transgenerational cycle of obesity and diabetes. *Diabetes* 2011;60(7):1849–1855. doi:10.2337/db11-0400, PMID:21709280.
- [31] Isganaitis E, Woo M, Ma H, Chen M, Kong W, Lytras A, *et al*. Developmental programming by maternal insulin resistance: hyperinsulinemia, glucose intolerance, and dysregulated lipid metabolism in male offspring of insulin-resistant mice. *Diabetes* 2014;63(2):688–700. doi:10.2337/db13-0558, PMID:24186867.
- [32] McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 2005;85(2):571–633. doi:10.1152/physrev.00053.2003, PMID:15788706.
- [33] Väärasmäki M, Pouta A, Elliott P, Tapanainen P, Sovio U, Ruokonen A, *et al*. Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. *Am J Epidemiol* 2009;169(10):1209–1215. doi:10.1093/aje/kwp020, PMID:19363101.
- [34] Crume TL, Ogden L, West NA, Vehik KS, Scherzinger A, Daniels S, *et al*. Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. *Diabetologia* 2011;54(1):87–92. doi:10.1007/s00125-010-1925-3, PMID:20953862.
- [35] Ma RC, Tutino GE, Lillycrop KA, Hanson MA, Tam WH. Maternal diabetes, gestational diabetes and the role of epigenetics in their long term effects on offspring. *Prog Biophys Mol Biol* 2015;118(1-2):55–68. doi:10.1016/j.pbiomolbio.2015.02.010, PMID:25792090.
- [36] Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, *et al*. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41(11):1105–1116. doi:10.1016/0895-4356(88)90080-7, PMID:3204420.
- [37] Mann JP, Valenti L, Scorletti E, Byrne CD, Nobili V. Nonalcoholic Fatty Liver Disease in Children. *Semin Liver Dis* 2018;38(1):1–13. doi:10.1055/s-0038-1627456, PMID:29471561.
- [38] Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001;60:5–20. doi:10.1093/bmb/60.1.5, PMID:11809615.
- [39] Wesolowski SR, Kasmi KC, Jonscher KR, Friedman JE. Developmental origins of NAFLD: a womb with a clue. *Nat Rev Gastroenterol Hepatol* 2017;14(2):81–96. doi:10.1038/nrgastro.2016.160, PMID:27780972.
- [40] Cao B, Liu C, Zhang Q, Dong Y. Maternal High-Fat Diet Leads to Non-alcoholic Fatty Liver Disease Through Upregulating Hepatic SCD1 Expression in Neonate Rats. *Front Nutr* 2020;7:581723. doi:10.3389/fnut.2020.581723, PMID:33282902.
- [41] Saengnipanthkul S, Noh HL, Friedline RH, Suk S, Choi S, Acosta NK, *et al*. Maternal exposure to high-fat diet during pregnancy and lactation predisposes normal weight offspring mice to develop hepatic inflammation and insulin resistance. *Physiol Rep* 2021;9(6):e14811. doi:10.14814/phy2.14811, PMID:33769706.
- [42] Peng H, Xu H, Wu J, Li J, Zhou Y, Ding Z, *et al*. Maternal high-fat diet disrupted one-carbon metabolism in offspring, contributing to nonalcoholic fatty liver disease. *Liver Int* 2021;41(6):1305–1319. doi:10.1111/liv.14811, PMID:33529448.
- [43] Forbes S, Taylor-Robinson SD, Patel N, Allan P, Walker BR, Johnston DG. Increased prevalence of non-alcoholic fatty liver disease in European women with a history of gestational diabetes. *Diabetologia* 2011;54(3):641–647. doi:10.1007/s00125-010-2009-0, PMID:21153530.
- [44] Lavrentaki A, Thomas T, Subramanian A, Valsamakis G, Thomas N, Toulis KA, *et al*. Increased risk of non-alcoholic fatty liver disease in women with gestational diabetes mellitus: A population-based cohort study, systematic review and meta-analysis. *J Diabetes Complications* 2019;33(10):107401. doi:10.1016/j.jdiacomp.2019.06.006, PMID:31326267.
- [45] Sattari M, Bril F, Egerman R, Kalavalapalli S, Cusi K. Relationship between non-alcoholic fatty liver disease during pregnancy and abnormal glucose metabolism during and after pregnancy. *J Invest Med* 2020;68(3):743–747. doi:10.1136/jim-2019-001186, PMID:31852748.
- [46] Lavrentaki A, Subramanian A, Thomas GN, Valsamakis G, Toulis K, Daly B, *et al*. Gestational Diabetes Mellitus is associated with increased risk of Non-Alcoholic Fatty Liver Disease: A population-based cohort study. *Endocrine Abstracts* 2018;56:GP92. doi:10.1530/endoabs.56.GP92.
- [47] Joueidi Y, Peoc'h K, Le Lous M, Bouzille G, Rousseau C, Bardou-Jacquet E, *et al*. Maternal and neonatal outcomes and prognostic factors in acute fatty liver of pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2020;252:198–205. doi:10.1016/j.ejogrb.2020.06.052, PMID:32622104.
- [48] Marjot T, Moolla A, Cobbald JF, Hodson L, Tomlinson JW. Nonalcoholic Fatty Liver Disease in Adults: Current Concepts in Etiology, Outcomes, and Management. *Endocr Rev* 2020;41(1):bnz009. doi:10.1210/edrv/bnz009, PMID:31629366.
- [49] Cioffi CE, Figueroa J, Welsh JA. Added Sugar Intake among Pregnant Women in the United States: National Health and Nutrition Examination Survey 2003–2012. *J Acad Nutr Diet* 2018;118(5):886–895.e1. doi:10.1016/j.jand.2017.10.021, PMID:29325892.
- [50] Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;307(5):491–497. doi:10.1001/jama.2012.39, PMID:22253363.
- [51] Lomas-Soria C, Reyes-Castro LA, Rodríguez-González GL, Ibáñez CA, Bautista CJ, Cox LA, *et al*. Maternal obesity has sex-dependent effects on insulin, glucose and lipid metabolism and the liver transcriptome in young adult rat offspring. *J Physiol* 2018;596(19):4611–4628. doi:10.1113/jp276372, PMID:29972240.
- [52] Sekkarie A, Welsh JA, Northstone K, Stein AD, Ramakrishnan U, Vos MB. 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] Kruse M, Seki Y, Vuguin PM, Du XQ, Fiallo A, Glenn AS, *et al*. High-fat intake during pregnancy and lactation exacerbates high-fat diet-induced complications in male offspring in mice. *Endocrinology* 2013;154(10):3565–3576. doi:10.1210/en.2012-1877, PMID:23861375.
- [54] Goldner D, Lavine JE. Nonalcoholic Fatty Liver Disease in Children: Unique Considerations and Challenges. *Gastroenterology* 2020;158(7):1967–1983.e1. doi:10.1053/j.gastro.2020.01.048, PMID:32201176.
- [55] Grossmann M, Wierman ME, Angus P, Handelsman DJ. Reproductive Endocrinology of Nonalcoholic Fatty Liver Disease. *Endocr Rev* 2019;40(2):417–446. doi:10.1210/er.2018-00158, PMID:30500887.
- [56] Sarkar M, Djerboua 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:33465483.
- [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 Herder WW, Dhatariya K, *et al* (eds). *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000. PMID:28121116.
- [58] Foulds CE, Treviño LS, York B, Walker CL. Endocrine-disrupting chemicals and fatty liver disease. *Nat Rev Endocrinol* 2017;13(8):445–457. doi:10.1038/nrendo.2017.42, PMID:28524171.
- [59] Yang 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):127–131.e2. doi:10.1016/j.cgh.2016.07.034, PMID:27523635.
- [60] Flemming JA, Mullin M, Lu J, Sarkar MA, Djerboua M, Velez MP, *et al*. Outcomes of Pregnant Women With Cirrhosis and Their Infants in a Population-Based Study. *Gastroenterology* 2020;159(5):1752–1762.e10. doi:10.1053/j.gastro.2020.07.052, PMID:32781083.
- [61] Westbrook RH, Yeoman AD, O'Grady JG, Harrison PM, Devlin J, Heneghan MA. 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.2011.03.036, PMID:21570482.
- [62] Sarkar M, Brady CW, Fleckenstein J, Forde KA, Khunger V, Molleston 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.31559, PMID:32946672.
- [63] Wang J, Li Z, Lin L. Maternal lipid profiles in women with and without gestational diabetes mellitus. *Medicine (Baltimore)* 2019;98(16):e15320. doi:10.1097/MD.00000000000015320, PMID:31008986.
- [64] Dyah AA, Rahadina R. Metabolic associated fatty liver disease and adverse maternal and fetal outcomes: a systematic review and meta-analysis. *Clin Exp Hepatol* 2021;7(3):305–311. doi:10.5114/ceh.2021.109228, PMID:34712833.
- [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 Gastroenterol* 2016;111(5):665–670. doi:10.1038/ajg.2016.43, PMID:26977755.
- [66] Mousa N, Abdel-Razik A, Shams M, Sheta T, Zakaria S, Shabana W, *et al*. Impact of non-alcoholic fatty liver disease on pregnancy. *Br J Biomed Sci* 2018;75(4):197–199. doi:10.1080/09674845.2018.1492205, PMID:29943682.
- [67] You SY, Han K, Lee SH, Kim MK. Nonalcoholic fatty liver disease and the risk of insulin-requiring gestational diabetes. *Diabetol Metab Syndr* 2021;13(1):90. doi:10.1186/s13098-021-00710-y, PMID:34446090.
- [68] Hagström H, Höijer J, Ludvigsson JF, Bottai M, Ekblom A, Hultcrantz R, *et al*. Adverse outcomes of pregnancy in women with non-alcoholic fatty liver disease. *Liver Int* 2016;36(2):268–274. doi:10.1111/liv.12902, PMID:26114995.
- [69] Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, *et al*. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. *J Gastroenterol Hepatol* 2009;24(7):1284–1288. doi:10.1111/j.1440-1746.2009.05831.x, PMID:19476560.
- [70] Stannes Kopp UM, Dahl-Jørgensen K, Stigum H, Frost Andersen L, Naess Ø, Nystad 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:22929211.
- [71] Sivan E, Homko CJ, Chen X, Reece EA, Boden G. Effect of insulin on fat metabolism during and after normal pregnancy. *Diabetes* 1999;48(4):834–838. doi:10.2337/diabetes.48.4.834, PMID:10102701.
- [72] Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, *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.
- [73] Lin J, Jiang X, Dong M, Liu X, Shen Q, Huang Y, *et al*. Hepatokine Pregnancy Zone Protein Governs the Diet-Induced Thermogenesis Through Activating Brown Adipose Tissue. *Adv Sci (Weinh)* 2021;8(21):e2101991. doi:10.1002/advs.202101991, PMID:34514733.
- [74] Herath RP, Siriwardana SR, Ekanayake CD, Abeysekera V, Kodithuwakku SUA, Herath HP. Non-alcoholic fatty liver disease and pregnancy complications among Sri Lankan women: A cross sectional analytical study. *PLoS One* 2019;14(4):e0215326. doi:10.1371/journal.pone.0215326, PMID:30978266.
- [75] Ajmera VH, Terrault NA, VanWagner LB, Sarkar M, Lewis CE, Carr JJ, *et al*. Longer lactation duration is associated with decreased prevalence of non-alcoholic fatty liver disease in women. *J Hepatol* 2019;70(1):126–132.

- 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] 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.
- [78] 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.
- [79] 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.
- [80] 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:25847730.
- [81] 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.
- [82] Butte NF, Hopkinson JM, Mehta N, Moon JK, Smith EO. Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. *Am J Clin Nutr* 1999;69(2):299–307. doi:10.1093/ajcn/69.2.299, PMID:9989696.
- [83] Gunderson EP, Jacobs DR Jr, Chiang V, Lewis CE, Feng J, Quesenberry CP Jr, *et al*. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-Year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). *Diabetes* 2010;59(2):495–504. doi:10.2337/db09-1197, PMID:19959762.
- [84] Houttu V, Csader S, Nieuwdorp M, Holleboom AG, Schwab U. Dietary Interventions in Patients With Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Front Nutr* 2021;8:716783. doi:10.3389/fnut.2021.716783, PMID:34368214.
- [85] Zhou Y, 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, Hanhineva 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, Omoto 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] Bae-Gartz I, 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, Vohlen C, Janoschek R, Schmitz L, *et al*. Maternal Exercise Mediates Hepatic Metabolic Programming via Activation of AMPK-PGC1 α Axis in the Offspring of Obese Mothers. *Cells* 2021;10(5):1247. doi:10.3390/cells10051247, PMID:34069390.
- [90] Franque SM, Bedossa P, Ratzliff 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, Ratzliff V, Loomba R, Rinella M, 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:31813633.
- [92] Huang SW, Ou YC, Tang KS, Yu HR, Huang LT, Tain YL, *et al*. Metformin 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.