

## Maternal obesity and metabolic (dysfunction) associated fatty liver disease in pregnancy: a comprehensive narrative review

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# Maternal obesity and metabolic (dysfunction) associated fatty liver disease in pregnancy: a comprehensive narrative review

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## ABSTRACT

**Introduction:** Obesity and metabolic-associated fatty liver disease (MAFLD) during pregnancy constitute significant problems for routine antenatal care, with increasing prevalence globally. Similar to obesity, MAFLD is associated with a higher risk for maternal complications (e.g. pre-eclampsia and gestational diabetes) and long-term adverse health outcomes for the offspring. However, MAFLD during pregnancy is often under-recognized, with limited management/treatment options.

**Areas covered:** PubMed/MEDLINE, EMBASE, and Scopus were searched based on a search strategy for obesity and/or MAFLD in pregnancy to identify relevant papers up to 2024. This review summarizes the pertinent evidence on the relationship between maternal obesity and MAFLD during pregnancy. Key mechanisms implicated in the underlying pathophysiology linking obesity and MAFLD during pregnancy (e.g. insulin resistance and dysregulated adipokine secretion) are highlighted. Moreover, a diagnostic approach for MAFLD diagnosis during pregnancy and its complications are presented. Finally, promising relevant areas for future research are covered.

**Expert opinion:** Research progress regarding maternal obesity, MAFLD, and their impact on maternal and fetal/offspring health is expected to improve the relevant diagnostic methods and lead to novel treatments. Thus, routine practice could apply more personalized management strategies, incorporating individualized algorithms with genetic and/or multi-biomarker profiling to guide prevention, early diagnosis, and treatment.

## ARTICLE HISTORY

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Maternal obesity; metabolic-associated fatty liver disease (MAFLD); metabolic dysfunction-associated steatotic liver disease (MASLD); nonalcoholic fatty liver disease (NAFLD); pregnancy; gestational diabetes mellitus (GDM); antenatal care



## 1. Introduction

### 1.1. Overview of obesity in pregnancy

Obesity is characterized by the accumulation of excess adipose tissue in the body, with the World Health Organization (WHO) defining overweight and obesity as a body mass index (BMI) over 25 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup>, respectively, for Caucasian adults [1]. During pregnancy, weight gain is expected due to changes in body composition and metabolism and the development of the placenta, amniotic fluid, and the growing fetus [2,3]. Guidelines for recommended gestational weight gain have been developed based on WHO categories of maternal BMI, as shown in Table 1 [4].

The increasing prevalence of obesity among women of reproductive age is a significant public health concern. In

2018, nearly 40 million pregnant women worldwide had a BMI in the overweight category [5]. This increasing trend poses a significant disease burden since maternal obesity and excessive gestational weight gain are linked to numerous adverse outcomes for both affected mothers and their offspring [6,7], including gestational diabetes mellitus (GDM; with GDM risk exhibiting a dose-response relationship with maternal obesity) [8,9], pre-eclampsia [10,11], preterm birth [12,13], the need for cesarean delivery [14,15], susceptibility to infections, and postpartum hemorrhage [16,17]. Moreover, long-term health complications for offspring include a higher risk of developing cardio-metabolic diseases later in life such as type 2 diabetes (T2DM), hypertension, and coronary heart disease [18–20].

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### Article highlights

- MAFLD is a growing concern among pregnant women, with prevalence rates which follow those of maternal obesity.
- Similarly to maternal obesity, MAFLD in pregnancy is also linked to a higher risk of adverse outcomes such as gestational diabetes, pre-eclampsia, and preterm birth, affecting both maternal and fetal health.
- The adverse effects of maternal MAFLD extend beyond the pregnancy period, potentially predisposing the offspring to long-term cardio-metabolic diseases, including obesity and type 2 diabetes.
- The complex pathophysiology of MAFLD involves insulin resistance, dysregulated adipokine secretion, and chronic inflammation, which are superimposed on normal pregnancy-related hormonal and metabolic changes.
- Diagnosing MAFLD in pregnancy may pose challenges due to overlapping symptoms with those often noted during pregnancy, and the limitations of current diagnostic methods. Non-invasive approaches combining biomarkers, scoring systems, and imaging techniques are key for diagnosing MAFLD in pregnancy.
- Research is needed to develop universally accepted diagnostic criteria and safe, effective treatment modalities for pregnant women. Advances in imaging, biomarker analysis, and understanding the gut-liver axis hold promise for personalized management strategies.
- Considering MAFLD assessment in pre-conception family planning and routine early screening during pregnancy could prompt timely interventions, reducing the incidence of gestational diabetes and other complications.

### 1.2. Overview of MAFLD in pregnancy

Metabolic dysfunction-associated fatty liver disease (MAFLD; or nonalcoholic fatty liver disease, NAFLD; or metabolic dysfunction-associated steatotic liver disease, MASLD, as recently proposed by a multi-society consensus statement) results from excess fat accumulation in hepatocytes and ranges from simple steatosis to steatohepatitis (nonalcoholic steatohepatitis, NASH; or metabolic dysfunction-associated steatohepatitis, MASH) with or without fibrosis [21]. The global prevalence of MAFLD parallels obesity rates, affecting up to 80–90% of adults with obesity [22], and increases with age [23]. Meta-analysis data suggest that MAFLD affects over 25% of the general adult population, with recent estimates indicating a prevalence of up to 22% in the 30–39 age range [24], further highlighting its prevalence among women of childbearing age [25].

Overall, MAFLD is the hepatic manifestation of central obesity and metabolic syndrome, posing a significant risk factor for cardiovascular disease (CVD) [26,27]. As with obesity, the pathogenesis of MAFLD is multifactorial, involving genetic, lifestyle, and other factors such as gut microbiota dysbiosis and altered intestinal permeability [28]. These may overlap with pregnancy, while it should be noted that the dynamic

hormonal and metabolic changes during pregnancy itself may contribute to hepatic changes across the pregnancy trimesters [25]. Thus, a fatty/steatotic liver during pregnancy is rather common in the context of MAFLD, while this may rarely be due to the acute fatty liver of pregnancy [25]. Data from the United States National Inpatient Sample (18,574,225 pregnancies, of which 5,640 had MAFLD) indicate a nearly three-fold increase in MAFLD prevalence during pregnancy from 2007 to 2015 (10.5 to 28.9 per 100,000 pregnancies) [29]. This underscores the high and rising prevalence of MAFLD in pregnant women, primarily driven by obesity, and the importance of early diagnosis and management [25].

## 2. Pathophysiologic mechanisms linking maternal obesity, MAFLD, and pregnancy

To better understand the underlying pathophysiology of MAFLD in the context of pregnancy, it is important to highlight key physiologic adaptations of the maternal metabolism and the unique role of the placenta during this period.

### 2.1. Key physiologic hormonal/metabolic adaptations during a normal pregnancy

Pregnancy involves profound and dynamic physiological changes in the maternal metabolism and the endocrine system (e.g. modified nutrient metabolism, energy homeostasis, and tissue sensitivity to insulin) to support the normal development and growth of the fetus through complex hormonal and metabolic pathways [30,31]. Initially, pregnancy is an ‘anabolic phase’ favoring energy storage, primarily in lipids, to meet the demands of the developing fetus and breastfeeding. During the first trimester, maternal glucose homeostasis is regulated by insulin, estrogen, and cortisol, prolonging blood glucose clearance, promoting adipose tissue deposition, and suppressing energy expenditure [32,33]. Gradually, pregnancy transitions into a ‘catabolic phase,’ or ‘fetal anabolic phase,’ using stored energy to nourish the growing baby. This metabolic shift is characterized by reduced insulin sensitivity, allowing glucose and free fatty acids to cross the placenta [31,34,35].

Overall, this gradual development of maternal insulin resistance during the progression of pregnancy is critical for securing an ample and continuous supply of glucose to the developing fetus, particularly during the third trimester [31,36]. A 50–60% reduction in insulin sensitivity occurs with advancing gestation in women with normal glucose tolerance and those with GDM [36,37]. Blood glucose levels decline as

**Table 1.** Guidelines regarding recommended gestational weight gain during pregnancy [4]. These guidelines are based on the World Health Organization (WHO) cutoff values for the different body mass index (BMI) categories, which were generated based on data mostly from Caucasian populations, and are intended for use among women in the USA (these may be applicable to women in other developed countries, but not to all women) [4].

	Pre-pregnancy body mass index (BMI)			
	Underweight	Normal weight	Overweight	Obesity
BMI (kg/m <sup>2</sup> )	<18.5	18.5–24.9	25–29.9	≥30
Total weight gain (range in kg)	12.5–18	11.5–16	7–11.5	5–9
Rates of weight gain (mean and range in kg/week) during the second and third trimester	0.51 (0.44–0.58)	0.42 (0.35–0.5)	0.28 (0.23–0.33)	0.22 (0.17–0.27)

pregnancy progresses, exacerbated by fasting, particularly during the third trimester, while fasting insulin levels significantly increase [31,38]. Maternal hepatic glucose production remains elevated, primarily through gluconeogenesis, as evidenced by a 30% rise in basal endogenous glucose production at 34–36 weeks compared to 12–14 weeks of gestation [31].

Moreover, pregnancy also induces significant physiologic changes in the maternal lipid metabolism, including adipose tissue accumulation and hyperlipidemia [39]. Elevated estrogen, progesterone, and insulin levels promote lipid deposition in early and mid-pregnancy, with increased fatty acid synthesis and lipoprotein lipase expression. Consequently, circulating levels of fatty acids, triglycerides, cholesterol, and phospholipids rise throughout pregnancy, peaking in the third trimester [31]. The catabolic state of the third trimester ceases further adipose tissue deposition, utilizing stored energy reserves to meet fetal demands, marked by increased hormone-sensitive lipoprotein lipase activity and enhanced lipolysis, particularly in fasting conditions [31,40]. Consequently, circulating free fatty acids levels rise, becoming the primary source of energy for the mother [31,40].

## 2.2. Key placental functions during a normal pregnancy

The placenta is a transient organ crucial for maternal and fetal well-being, adapting to the physiological needs of both [41]. To that aim, specialized trophoblast cells are positioned within the maternal-fetal interface in the placenta to sustain fetal viability by mirroring the physiological status of both the mother and the fetus, and continually responding to environmental cues [9]. Thus, the placenta facilitates nutrient exchange, oxygen provision, and waste elimination, including carbon dioxide [33]. It regulates fetal growth by synthesizing numerous hormones and signaling molecules (e.g. estrogen, progesterone, human chorionic gonadotropin, human placental lactogen, leptin, and relaxin) [42]. The production of estrogen and progesterone increases exponentially after the sixth week of pregnancy as ovarian production of these sex steroids declines. Estrogen effects play a critical role in pregnancy by enhancing the receptor-mediated uptake of low-density lipoprotein cholesterol, a precursor for placental steroids [43]. Additionally, estrogen increases the uteroplacental blood flow, which facilitates nutrient and oxygen delivery to the growing fetus, and stimulates endometrial prostaglandin synthesis, which helps maintain the pregnancy and prepare the uterine lining for childbirth [36].

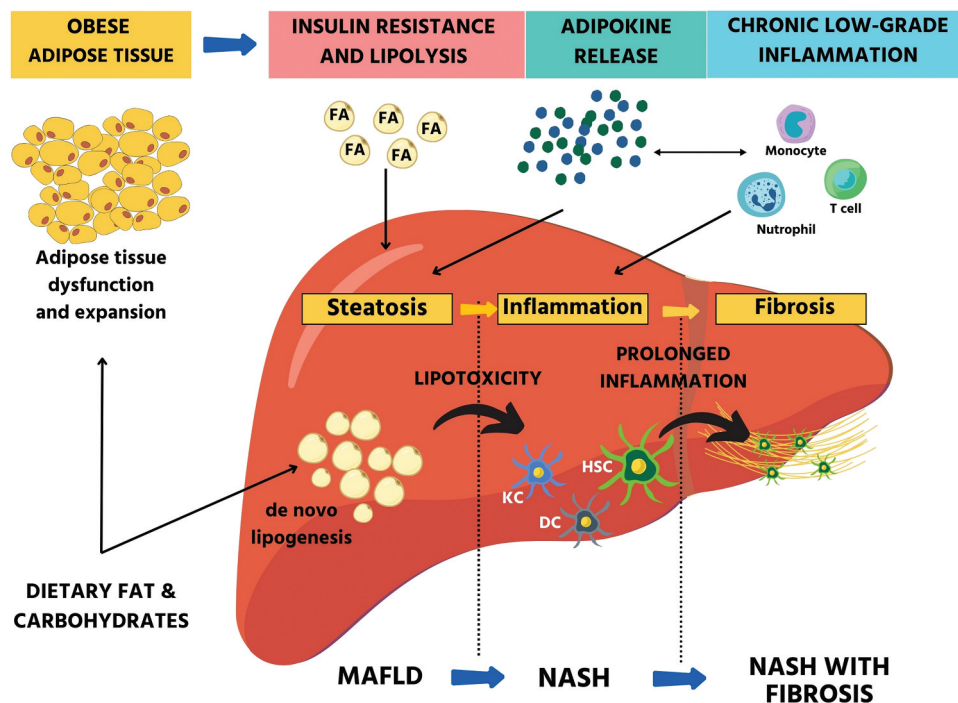
Crucially for a healthy pregnancy, glucose serves as the primary energy substrate for the fetal-placental unit, with fetal energy provision depending on placental glucose transport [33,44]. This transport is primarily achieved via diffusion mediated by the glucose transporter-1 (GLUT1), which shows a 3-fold greater density in the microvilli membrane [45,46]. Furthermore, the placenta also plays a key role in the development of insulin resistance during pregnancy through the placental lactogen secretion, modulating insulin sensitivity and contributing to physiological hyperglycemia [47]. This hormone also exhibits lipolytic properties, peaking in the second half of pregnancy [47].

## 2.3. Interplay between maternal obesity, insulin resistance, inflammation and MAFLD

Building upon the aforementioned physiologic adaptations of the maternal metabolism during pregnancy, a complex interplay of underlying pathophysiologic mechanisms/pathways appears to link adipose tissue accumulation with MAFLD and other related cardio-metabolic complications (e.g. GDM) in pregnant women with obesity. Indeed, although the full spectrum of links between maternal obesity, MAFLD, and subsequent hyperglycemia are not fully understood, insulin resistance appears to be a cornerstone in the pathophysiology of both hepatic steatosis and central obesity, which subsequently impacts on glucose metabolism during pregnancy and even postpartum (Figure 1) [48].

Further potential pathophysiologic mechanisms include the development of a persistent, low-grade inflammation that can follow excess adipose tissue accumulation centrally and in the liver [49,50]. As such, increased circulating levels of pro-inflammatory adipokines, chemokines, and cytokines (e.g. tumor necrosis factor- $\alpha$ , and interleukin-6) from the adipose tissue and the liver are associated with the development and the severity of insulin resistance, MAFLD, and GDM [51]. Leptin, the prototype adipokine, plays a crucial role in linking obesity and MAFLD by regulating appetite and energy balance [52]. Elevated leptin levels characterize obesity and are considered to contribute to hepatic steatosis and inflammation [52]. A summary of key adipokines that are considered to play a role in MAFLD pathogenesis is presented in Table 2 [51]. Interestingly, the triggering of pro-inflammatory pathways and immune cell infiltration of the expanded adipose tissue in obesity appears to be also mirrored in the steatotic liver where chemokines/cytokines promote hepatic infiltration by circulating immune cells (e.g. neutrophils, monocytes, and T-lymphocytes) and the activation of local Kupffer and hepatic stellate cells. The latter appears to play a key role in the development of fibrosis in the context of MAFLD [51].

It is also noteworthy that, in response to obesity and high-fat diets, hepatocytes exhibit a dysregulated lipid metabolism, which is primarily characterized by enhanced free fatty acid uptake and *de novo* lipogenesis, as well as diminished fatty acid  $\beta$ -oxidation and very low-density lipoprotein secretion [53–55]. Indeed, the pathophysiology of MAFLD is intricately linked to adipose tissue dynamics, with the expansion of white adipose tissue depots in obesity leading to adipocyte dysfunction and insulin resistance, which further trigger lipolysis [50]. This results in higher circulating fatty acid levels, which, together with the aforementioned dysregulated adipokines, favor pro-steatogenic effects and intrahepatic fat accumulation [51]. Furthermore, a high intake of dietary fat and carbohydrates, which is common in obesity, further amplifies *de novo* lipogenesis and fat accumulation in the liver [55,56]. Notably, ectopic accumulation of triglyceride-derived toxic metabolites may result in lipotoxicity and cellular dysfunction marked by endoplasmic reticulum, oxidative stress, and mitochondrial defects. Subsequently, lipotoxic effects and/or increased endoplasmic reticulum stress in the liver can trigger hepatocellular injury with inflammation, apoptosis, autophagy, and fibrosis [57,58]. Interestingly, MAFLD seems to frequently



**Figure 1.** Simplified representation of key mechanisms which appear to be implicated in the pathogenesis of metabolic-associated fatty liver disease (MAFLD); adopted from Kyrou et al., 2018 [50], and Francisco et al., 2022 [51]. Excess white adipose tissue accumulation in obesity promotes adipocyte dysfunction and systemic insulin resistance, leading to increased lipolysis. Consequently, increased and/or dysregulated circulating fatty acids (FA) and adipokine levels contribute to intrahepatic fat accumulation (steatosis). Hepatic steatosis can be further amplified by dietary factors, such as a high fat and carbohydrate intake, augmenting de novo lipogenesis (DNL). Excess/ectopic accumulation of triglycerides (TGs) and their derived toxic metabolites induces lipotoxicity, cellular dysfunction (including endoplasmic reticulum stress, oxidative stress, and mitochondrial defects), lipoapoptosis, and activation of inflammatory pathways locally. Adipose tissue expansion also increases chemoattractants and promotes immune cell infiltration, which together with dysregulated adipokine secretion, contribute to the development of a chronic low-grade inflammation both locally (e.g. within adipose tissue depots and the liver) and systemically. In addition, hepatic infiltration by circulating immune cells (neutrophils, monocytes, T-lymphocytes) occurs, alongside activation of resident liver cells such as Kupffer cells (KCs), dendritic cells (DCs), and hepatic stellate cells (HSCs). Persistent inflammation can ultimately trigger fibrogenesis, with HSCs playing a key role in this process.

precede the development of skeletal muscle lipid deposition and macrophage infiltration, as well as extrahepatic insulin resistance and hyperglycemia, thereby positioning hepatic steatosis as one of the initial dominos in the cascade of the cardio-metabolic disorders comprising the metabolic syndrome [55,59].

It is evident that superimposing this complex pathophysiologic interplay between maternal obesity and MAFLD on the dynamic physiologic adaptations during pregnancy creates an environment that may further favor insulin resistance, dyslipidemia, and chronic low-grade inflammation, which may, in turn, lead to complications such as GDM.

Current research aims to clarify the spectrum of mediating factors within this interplay, and thus potentially lead to novel interventions against MAFLD. For example, recent research suggests a link between the gut microbiota and chronic liver diseases, including MAFLD [60]. Indeed, gut microbiota imbalances may result in increased intestinal permeability, further exposing the liver to pro-inflammatory factors. This is supported by clinical studies which have shown correlations between MAFLD and circulating levels of endotoxin (or lipopolysaccharide, a component of the exterior cell wall of gram-negative bacteria which is a known pyrogen), suggesting a link between the gut microbiome and hepatic health [61]. Moreover, animal studies have demonstrated that prebiotic supplementation may mitigate MAFLD by inhibiting the fatty

acid synthesis pathway [61]. Modifying the gut microbiota with probiotics has also shown positive outcomes in MAFLD mice [62], while encouraging results have also been documented in both adults and children with MAFLD who responded favorably to interventions with probiotics [63]. Interestingly, meta-analysis data from 15 randomized controlled trials involving 782 patients with MAFLD demonstrated that a combination of probiotics and prebiotics might have a significant impact on reducing insulin resistance and hepatic steatosis and stiffness, as well as tumor necrosis factor- $\alpha$  expression and transaminase, low-density lipoprotein, triglyceride, and cholesterol levels [64]. Overall, the exact role of the gut microbiota in MAFLD pathophysiology is still under investigation, aiming to offer novel insight into the underlying pathophysiologic mechanisms and the potential use of prebiotics and probiotics for MAFLD treatment.

### 3. MAFLD diagnosis during pregnancy

The alarming rise of MAFLD prevalence globally highlights the need for early MAFLD detection with reliable diagnostic tools in pregnant women, especially in the presence of obesity.

Currently, liver biopsy is the gold standard for diagnosing and staging MAFLD, but its invasiveness and associated risks make it unsuitable for routine screening and use during pregnancy [65]. Consequently, noninvasive diagnostic methods are

**Table 2.** Selected adipokines with a potential role in the pathophysiology of metabolic-associated fatty liver disease (MAFLD) [51].

Adipokine	Description	Receptor/Signaling	Functions
Leptin	Cytokine-like hormone encoded by the LEP gene, secreted by various tissues	LEP-R (encoded by <i>LEPR</i> ) with multiple isoforms; signals via JAK-STAT, p38 MAPK, JNK, ERK1/2, PI3K/Akt, or PKC	Controls appetite and body weight, regulates insulin secretion, thermogenesis, lipid homeostasis, reproductive functions, inflammation, infection, angiogenesis, and cartilage/bone homeostasis
Adiponectin	Encoded by the <i>ADIPOQ</i> gene, homologous to C1q, collagen VIII, and collagen X; it exists in various forms	AdipoR1 (skeletal muscle) and AdipoR2 (liver); signals through AMPK, PPAR, or PPAR	Augments fatty acid oxidation and glucose uptake in muscle, decreases glucose synthesis in the liver, and affects obesity, metabolic syndrome, lipodystrophy, and cardiovascular disease
Resistin	Found as dimers in human blood, produced in macrophages, mononuclear leukocytes, bone marrow cells, and spleen	Potential receptors include ROR-1, IGF-1 R, and CAP1; TLR4 mediates pro-inflammatory cytokines secretion	Regulates blood glucose levels and lipid metabolism, promotes insulin resistance, induces pro-inflammatory cytokines secretion, and monocytes differentiation into macrophages
RBP4	Member of the lipocalin family, expressed in various tissues	Bound to TTR in circulation, STRA6 mediates retinol influx	Transports retinol, contributes to insulin resistance, dyslipidemia, T2DM, and cardiovascular dysfunction
Visfatin	Homodimeric cytokine-like peptide with intracellular and extracellular forms	Unidentified specific receptor; iNAMPT modulates cellular metabolism, and eNAMPT induces pro-inflammatory cytokine production	Modulates cellular metabolism, differentiation, and stress response; associates with metabolic and inflammatory diseases
Chemerin	Secreted as an inactive precursor, activated by various proteases	CMKLR1 mediates chemotactic activity, GPR1, and CCRL2 bind chemerin	Regulates adipocyte differentiation, insulin sensitivity, glucose, and lipid metabolism; bridges innate and adaptive immunity through CMKLR1
AFABP	Belongs to the lipocalin family, abundant cytosolic protein in mature adipocytes	Unidentified receptor, induced by various factors	Modulates adipocyte lipolysis, promotes cholesterol esters accumulation and foam-cell formation, and induces endothelial dysfunction

ADIPOQ: Adiponectin; AdipoR1: Adiponectin Receptor 1; AdipoR2: Adiponectin Receptor 2; AFAB: Adipocyte Fatty Acid-Binding Protein; AMPK: AMP-activated Protein Kinase; CAP1: Cyclase-associated Protein 1; CCRL2: Chemokine Receptor-Like 2; CMKLR1: Chemokine-Like Receptor 1; eNAMPT: Extracellular Nicotinamide Phosphoribosyltransferase; ERK1/2: Extracellular signal-Regulated Kinases 1 and 2; GPR1: G Protein-Coupled Receptor 1; IGF-1 R: Insulin-like Growth Factor 1 Receptor; iNAMPT: Intracellular Nicotinamide Phosphoribosyltransferase; JAK-STAT: Janus Kinase-Signal Transducer and Activator of Transcription; JNK: c-Jun N-terminal Kinase; LEP: Leptin; LEP-R: Leptin Receptor; MAPK: Mitogen-Activated Protein Kinase; PI3K/Akt: Phosphoinositide 3-Kinase/Protein Kinase B; PKC: Protein Kinase C; PPAR: Peroxisome Proliferator-Activated Receptor; RBP4: Retinol-Binding Protein 4; ROR-1: Receptor Tyrosine Kinase-like Orphan Receptor 1; STRA6: Stimulated by Retinoic Acid Gene 6; TLR4: Toll-Like Receptor 4; TTR: Transthyretin.

typically utilized during pregnancy. These methods include various biomarkers, scoring systems, and imaging techniques which can be combined based on clinical indications and availability within clinical practice pathways and antenatal care [65]. The use of such noninvasive methods is essential to minimize risk to both mother and fetus.

In this context, a noninvasive multi-step diagnostic approach considers medical history (e.g. maternal obesity, gestational diabetes) and employs MAFLD biomarkers and scoring systems. Key biomarkers and scoring systems include the NAFLD Activity Score (NAS), the Enhanced Liver Fibrosis (ELF) test, the Fibrosis-4 index (FIB-4), the NAFLD Fibrosis Score (NFS), and the aspartate aminotransferase to platelet ratio index (APRI) [66–69]. Imaging techniques such as ultrasonography and the ultrasound-based controlled attenuation parameter (CAP) integrated into FibroScan are utilized for risk stratification and diagnosis [66–69].

Additional MAFLD-related scores/indices used in clinical practice and/or research settings include the Fatty Liver Index (FLI), the NAFLD Liver Fat Score (NLFS), and the Lipid Accumulation Product (LAP) [70–74]. These are typically inexpensive and easy to obtain/calculate based on available clinical and laboratory data, and can be used with available imaging methods. For instance, the FLI has been proposed as a screening tool for MAFLD in the general population and is being tested for predicting MAFLD in pregnancy, particularly during the first trimester [75]. Current research also focuses on novel biomarkers such as thrombospondin 2 [65], non-coding RNAs (e.g. miR-122) [65], and urinary peptides [76]. A summary of additional biomarkers/indices used for MAFLD is presented in Table 3.

Despite advances in biomarker development, these noninvasive methods have limitations in sensitivity and specificity, particularly for detecting early and moderate fibrosis. Therefore, imaging methods are often employed to complement biomarker data [69,77–80]. Among these, b-mode ultrasonography is the most widely used imaging method due to its ease of operation and cost-effectiveness [65], though its accuracy is limited in detecting hepatic fat (<20), particularly in obese patients [69,79]. To address this limitation, ultrasonography-based scoring systems have been developed, demonstrating better diagnostic performance in individuals with obesity [65]. Furthermore, the controlled attenuation parameter (CAP), derived from ultrasound signals, is increasingly applied – depending on availability – to detect hepatic steatosis, albeit with varying accuracy depending on the experience/skills of the operator and the presence of severe obesity [65]. In addition, computed tomography (CT) provides relatively broad availability and high accuracy, but its use is limited by radiation exposure [65,69]. Finally, proton magnetic resonance spectroscopy and magnetic resonance imaging (MRI) based methods, such as the MRI-proton density fat fraction (MRI-PDFF, which reflects the triglyceride concentration within the hepatic tissue), offer high accuracy and sensitivity in diagnosing all stages of steatosis [69]; however, their use is restricted due to their high cost and the requirement for specialized equipment, sophisticated algorithms, and expert operators [65].

Overall, selecting an accurate and safe diagnostic approach for early MAFLD diagnosis in pregnant women is challenging. A summary of the diagnostic methods is presented in Table 4.

**Table 3.** Selected biomarkers/indices used in the context of metabolic-associated fatty liver disease (MAFLD) [65].

Category	Biomarker Type	Biomarkers/Indices/Factors
General fatty liver diagnosis	Indices and Serum/Plasma	Waist circumference, BMI, triglycerides, $\gamma$ -glutamyl transferase ALT/AST, BMI, sex, type 2 diabetes presence Triglycerides, cholesterol, $\gamma$ -glutamyl transferase, ALT, AST
	Omics-based	Basal hemoglobin Bile acids/glutathione Short-chain fatty acids/eicosanoids
Steatohepatitis/Inflammation specific	Serum/Plasma	Cytokeratin-18 Fibroblast growth factor 12, CK-18 C-reactive protein, TNF, IL-6, IL-1, IL-1RA, CXCL10 Activated plasminogen activator inhibitor 1
	Omics-based	Hydroxyoctadecadienoic acid 9 and 13, oxo-octadecadienoic acids Linoleic acid/hydroxyoctadecadienoic acid 13
Fibrosis	Noncoding RNA	miR-122, miR-192, miR-16, miR-21, miR-27b, miR-197, miR-34a, miR-375, miR-451, etc.
	Indices and Serum/Plasma	AST/ALT, AST/platelet ratio Age, AST, ALT, platelet count BMI, AST/ALT, diabetes presence Age, diabetes presence, BMI, platelets, albumin, AST/ALT Hyaluronic acid, metalloprotease-1 inhibitor, procollagen III amino-terminal peptide Pro-C3, Laminin
	Noncoding RNA	miR-122, miR-192, miR-16, miR-21, miR-27b, miR-197, miR-30c, lncRNA APTR, lncRNA RP11-128N14.5, lncRNA GAS5

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CK-18: Cytokeratin-18; CXCL10: C-X-C Motif Chemokine Ligand 10; FGF12: Fibroblast Growth Factor 12; IL-1: Interleukin 1; IL-1RA: Interleukin 1 Receptor Antagonist; IL-6: Interleukin 6; lncRNA: Long Noncoding RNA; miR: microRNA; PAI-1: Plasminogen Activator Inhibitor 1; TNF: Tumor Necrosis Factor;  $\gamma$ -GT: Gamma-Glutamyl Transferase.

**Table 4.** Diagnostic approaches for MAFLD during pregnancy.

Test Type	Method	Description	Limitations
Imaging	B-mode Ultrasonography	Widely available, easy to operate, cost-effective	Limited accuracy in obesity, low hepatic fat detection
	CAP	Uses ultrasound signals to detect hepatic steatosis	Varies with operator skill, less accurate in severe obesity
	MRI-Proton Density Fat Fraction (MRI-PDFF)	High accuracy and sensitivity for all steatosis stages	High cost, requires specialized equipment and expertise
	CT scan	Broad availability, high accuracy	Limited by radiation exposure
Biomarkers/Scoring	NAFLD Activity Score (NAS)	Composite score based on liver biopsy findings	Invasive, not suitable for routine screening
	Enhanced Liver Fibrosis (ELF) Test	Blood test measuring fibrosis markers	Limited availability, cost
	Fibrosis-4 Index (FIB-4)	Non-invasive scoring based on age, AST, ALT, platelet count	Moderate accuracy for fibrosis detection
	NAFLD Fibrosis Score (NFS)	Composite score using clinical and laboratory data	Moderate accuracy, can miss early/moderate fibrosis
	AST to Platelet Ratio Index (APRI)	Simple blood test combining AST and platelet count	Limited sensitivity/specificity for early fibrosis
	Fatty Liver Index (FLI)	Estimates hepatic steatosis based on BMI, waist circumference, triglycerides, GGT	Being tested for use in pregnancy, moderate accuracy
	NAFLD Liver Fat Score (NLFS)	Uses AST, AST/ALT ratio, fasting insulin levels	Requires fasting sample, limited by patient compliance
Novel Biomarkers	Lipid Accumulation Product (LAP)	Surrogate index for central obesity using waist circumference, triglycerides	May be less reliable in varying populations
	Thrombospondin 2	Emerging biomarker for liver fibrosis	Early research stage, limited validation
	Non-coding RNAs (e.g. miR-122)	Potential for noninvasive MAFLD diagnosis	Early research stage, requires further validation
	Urinary peptides	Biomarkers for liver fibrosis	Early research stage, limited clinical application

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CAP: Controlled Attenuation Parameter; GGT: Gamma-Glutamyl Transferase; MAFLD: metabolic-associated fatty liver disease; NAFLD: nonalcoholic fatty liver disease.

Ultrasound is the most common first-line choice, followed by transient liver elastography and noninvasive scores, depending on availability. MAFLD severity can also be assessed using surrogate steatosis, inflammation, and fibrosis biomarkers alongside routine antenatal care tests. However, there is no consensus on the optimal timing for assessing MAFLD during pregnancy. This lack of standardized guidelines highlights the need for further research to determine the most appropriate periods for screening and diagnosis. Early identification of MAFLD can potentially improve management

strategies and outcomes, emphasizing the importance of establishing clear protocols for timing assessments.

### 3.1. Considering other abnormal findings of liver disease in pregnancy

For MAFLD diagnosis as part of antenatal care pathways, certain aspects of potential liver disease during the gestation period should also be considered, as outlined in the following sections.

**Table 5.** Reference ranges for routine liver function tests for non-pregnant women and each pregnancy trimester [81].

LFTs	Non-pregnant	1 <sup>st</sup> pregnancy trimester	2 <sup>nd</sup> pregnancy trimester	3 <sup>rd</sup> pregnancy trimester
ALT (IU/L)	0–40	6–32	6–32	6–32
AST (IU/L)	7–40	10–28	11–29	11–30
Bilirubin (μmol/L)	0–17	4–16	3–13	3–14
GGT (IU/L)	11–50	5–37	5–43	3–41
ALP (IU/L)	30–130	32–100	43–135	133–418
Albumin (g/L)	35–46	28–37	–	–

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyl Transferase; IU/L: International Units per Liter; LFTs: Liver Function Tests.

### 3.2.1. Abnormal liver function tests in pregnancy

Abnormal liver function tests (LFTs) are of limited diagnostic value for MAFLD during pregnancy since these are not MAFLD-specific. Indeed, LFTs are not routinely performed during pregnancy unless clinically indicated, since the normal levels of LFTs range depending on the pregnancy trimester, as presented in Table 5 [81,82]. For example, ALT and GGT are about 20% lower in pregnant women, while alkaline phosphatase increases due to placental production [83].

Abnormal maternal LFTs during pregnancy are often associated with obstetric complications, such as the HELLP (Hemolysis-Elevated Liver enzymes-Low Platelets) syndrome, pre-eclampsia, acute fatty liver, intrahepatic cholestasis, and hyperemesis gravidarum [81]. Furthermore, infectious hepatitis, primarily by hepatotropic viruses, may cause abnormal LFTs in pregnant women (e.g. hepatitis B can cause elevated ALT levels during pregnancy) [84], while other non-obstetric causes include drug-induced liver injury and autoimmune hepatobiliary diseases [81]. Interestingly, some studies link elevated liver enzymes in pregnancy with adverse outcomes, such as GDM (e.g. increased gamma-glutamyl transferase and alanine aminotransferase levels may correlate with GDM risk) [63–66] and pre-eclampsia (e.g. elevated transaminase levels may be associated with severe pre-eclampsia) [85].

### 3.2.2. Acute fatty liver of pregnancy

In contrast to MAFLD, which is common in pregnant women with obesity, the acute fatty liver of pregnancy (AFLP) is a rare liver disease during pregnancy [25]. AFLP constitutes a serious complication that may develop primarily in the third pregnancy trimester, although it may also manifest in the second trimester or postpartum [25,86]. The incidence of AFLP is relatively low (approximately 5–20 cases per 100,000 pregnancies), presenting more frequently in pregnant women with a history of AFLP in prior pregnancies or multiple gestations [87].

AFLP is characterized by impaired fatty acid metabolism, leading to oxidative damage in the maternal liver. The initial symptoms of AFLP are often nonspecific (e.g. nausea and abdominal pain), but can progress to signs/symptoms indicative of acute liver failure, including jaundice, hypoglycemia, and hepatic encephalopathy, and significant bleeding, with potentially fatal complications for both the mother and the fetus. Laboratory findings in AFLP typically include elevated aminotransferases and bilirubin levels, as well as leukocytosis and coagulopathy, underscoring the urgency for prompt diagnosis and treatment [25,88]. As noted for MAFLD, research is currently directed to improving diagnostic techniques/methods for AFLP (e.g. liver stiffness assessment via noninvasive methods) in order to enhance early AFLP detection in clinical practice [25,86].

### 3.2.3. Cirrhosis in pregnancy

As the prevalence of MAFLD among pregnant women is increasing, a parallel increase has been noted in the rates of cirrhosis during pregnancy [89]. However, estimates specific to MAFLD-related cirrhosis in pregnancy are broadly lacking [90]. Interestingly, a recent population-based retrospective cohort study by Sarkar *et al.* [90] showed that the incidence rate of pregnancies with MAFLD cirrhosis increased from 1/1,000 in 2000 to 1.7/1,000 in 2016, while non-MAFLD cirrhosis exhibited a less marked rise from 48.6/100,000 in 2000 to 53.7/100,000 in 2016. Furthermore, MAFLD accounted for the majority (72.5%) of pregnancies with cirrhosis by the end of that study, suggesting that the increase of cirrhosis in pregnancy is largely driven by MAFLD [90]. It should be noted that in that study, compared to those with non-MAFLD cirrhosis, women with MAFLD-related cirrhosis were slightly younger at conception, more likely to be rural-based, and less likely to have prior decompensation, while more often had obesity, dyslipidemia, and hypertension. Moreover, MAFLD cirrhosis was associated with a higher relative risk of hypertensive complications, although this was attenuated in multivariate analysis [90]. Finally, regarding infant outcomes in the same study, MAFLD cirrhosis was associated with a lower relative risk of preterm birth and small for gestational-age infants but with an increased risk of large for gestational-age infants [90]. As MAFLD-related cirrhosis in pregnancy is expected to follow the increasing prevalence of MAFLD, such liver complications should not be underestimated in the care of pregnant women with maternal obesity and MAFLD. Varices are a significant complication in cirrhotic patients, with an estimated prevalence of 30–40% at the time of depending on location and diagnosis [91]. The development of varices in MAFLD-related cirrhosis may be influenced by factors such as the severity of liver fibrosis and the presence of metabolic risk factors, including obesity and diabetes [92]. Regular screening through endoscopy is recommended to detect varices early and prevent bleeding, which can be life-threatening [93,94]. The prognosis for patients with MAFLD-related cirrhosis and varices depends on effective control of bleeding episodes and management of the underlying liver disease and associated metabolic conditions [95].

## 4. MAFLD, obesity, and pregnancy complications

The existing body of research illustrates that obesity and related metabolic dysfunctions, such as those seen in MAFLD, exacerbate pregnancy complications. There is a dose-response relationship between increasing obesity severity and severe maternal morbidity; women with class III and more severe obesity (BMI  $\geq 50$  kg/m<sup>2</sup>) face significantly higher risks, including renal failure, air and thrombotic embolism, blood

transfusion, heart failure, and mechanical ventilation [96]. Additionally, increasing maternal weight is linked to a higher risk of late-onset preeclampsia with severe features [97] and women with extreme obesity (pre-pregnancy BMI  $\geq 50$  kg/m<sup>2</sup>) have heightened risks of gestational hypertension, GDM, Caesarean section, prolonged hospital stays, and adverse neonatal outcomes such as macrosomia [98]. These complications are exacerbated by the presence of MAFLD, which further impairs metabolic regulation and liver function [97,98].

Indeed, pregnant women with MAFLD exhibit an increased risk of GDM, hypertensive complications, cesarean delivery, and postpartum hemorrhage, as well as higher rates of pre-term and small or large for gestational age births [99,100]. Overall, the risk of adverse pregnancy outcomes appears to be higher in pregnant women with maternal obesity and MAFLD (Figure 2), highlighting the importance of considering metabolic health in pregnant women, particularly when maternal obesity is noted during the first antenatal care visit [101]. Therefore, the significant overlap between obesity, metabolic syndrome, MAFLD, and adverse pregnancy outcomes emphasizes the need for comprehensive preconception counseling and targeted interventions to manage MAFLD and related metabolic conditions to improve pregnancy outcomes.

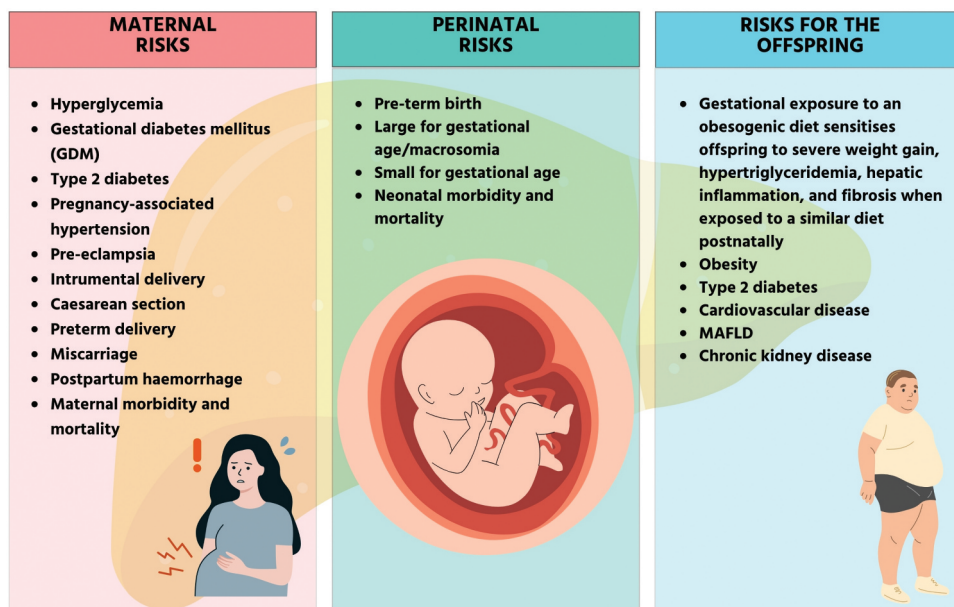
#### 4.1. MAFLD and GDM risk

It is particularly noteworthy that a bidirectional association appears to exist between MAFLD and GDM. As such, MAFLD predicts the development of GDM during pregnancy, with this relationship remaining significant even after adjusting for multiple confounders [25]. Moreover, a meta-analysis by El Jamaly et al. [102], which included 22 studies and 13,641 female

patients with MAFLD, showed that MAFLD exhibits a positive association with significantly increased maternal diabetic complications. This is in accord with meta-analysis data from Dyah et al. [103], which also revealed that MAFLD was linked to an increased risk of hyperglycemia. Similarly, a prospective cohort study by Koralegedara et al. [104] identified MAFLD as a significant predictor of GDM, with the cumulative incidence of GDM increasing with the severity of fatty liver even after adjusting for age and other known risk factors. Therefore, routine early identification of MAFLD during pregnancy may help prompt early screening for GDM.

#### 4.2. MAFLD and risk of cardiovascular pregnancy complications

Physiological changes during pregnancy, such as increases in circulatory volume and insulin resistance, as well as pro-inflammatory responses and dyslipidemia, can predispose to the development of cardiovascular complications during pregnancy [102]. Pregnant women with MAFLD face an even greater risk of such complications, especially in the presence of maternal obesity, as documented by multiple systematic reviews and meta-analyses [100,102,103]. For instance, a prospective study by Jung et al. examined the relationship between MAFLD and pregnancy-associated hypertension, including gestational hypertension, preeclampsia, or eclampsia, and found a significantly higher risk in pregnant women with MAFLD, with grade 2–3 steatosis remaining a significant predictor even after adjusting for other known metabolic risk factors [105]. Similarly, a cross-sectional study in Sri Lanka by Herath et al. [106] showed that pregnant women with MAFLD hold a twofold higher risk of developing gestational hypertension



**Figure 2.** Summary of maternal and offspring complications associated with maternal obesity and metabolic-associated fatty liver disease (MAFLD) during pregnancy. MAFLD predisposes pregnant women to metabolic dysregulation, including hyperglycemia, GDM, and pregnancy-associated hypertensive disorders. In addition, there is an increased of obstetric complications, such as instrumental delivery and cesarean section, alongside preterm delivery, miscarriage, and postpartum hemorrhage. Moreover, offspring exposed to MAFLD in utero experience increased susceptibility to adverse cardio-metabolic programming, manifesting as early weight gain, hypertriglyceridemia, hepatic inflammation, and fibrosis later in life with increased risk for obesity, MAFLD, type 2 diabetes, cardiovascular and kidney disease.

and pre-eclampsia, even after controlling for variables such as BMI, age, and hyperglycemia in pregnancy. Collectively these findings suggest that sonographic evidence of MAFLD early during pregnancy may independently predict the risk of developing gestational hypertension, preeclampsia, or eclampsia.

These emerging data may have further implications for routine practice. For example, clinical guidelines recommend low-dose aspirin initiation in the late first trimester for pregnant women at high risk of pre-eclampsia, considering factors such as history of pre-eclampsia, multifetal gestation, chronic hypertension, preexisting diabetes, renal disease, and autoimmune diseases [107]. Thus, based on the aforementioned findings, such as those by Jung *et al.*, it could be suggested that pregnant women with MAFLD may also benefit from low-dose aspirin prophylaxis [105]. However, well-designed randomized controlled studies are needed to validate whether such interventions with low-dose aspirin administration early in pregnancy may be effective against pregnancy-associated hypertension in pregnant women with MAFLD.

#### 4.3. MAFLD and other pregnancy complications

Pregnant women with MAFLD exhibit an increased risk of additional adverse fetal outcomes, such as preterm birth, primarily linked to maternal obesity [99,100]. Thus, macrosomia and large for gestational age infants may be the result of fetal overgrowth due to increased maternal levels of glucose and free fatty acids. The meta-analysis by Dyah *et al.*, which included six studies with 20,535,994 pregnant women (5,964 with MAFLD), showed that maternal MAFLD was significantly associated with increased risk of preterm birth and the need for Caesarean section but not with the large for gestational age risk [103]. Notably, pregnant women with MAFLD have been shown to also exhibit a greater incidence of postpartum hemorrhage compared to those without (6% vs. 3–5%, respectively) [108]. Furthermore, fatty liver on ultrasound scan has been reported as a significant risk factor for early pregnancy miscarriages [104]. Finally, another study by Hagström *et al.* [100] using data from the Swedish Medical Birth Register showed that women with MAFLD exhibited increased risk not only for GDM and pre-eclampsia, but also for preterm birth, low birth weight, and the need for Caesarean section, independently of BMI and diabetes [100]. This highlights the potential independent impact of MAFLD on these adverse pregnancy outcomes. Thus, although further data are still required, MAFLD emerges as a significant risk factor for key obstetric complications, prompting considerations for pre-conception counseling and tailored monitoring during antenatal care.

#### 4.4. Maternal obesity, MAFLD, and risks/complications for the offspring

Maternal obesity and/or excess weight gain during pregnancy have been linked to various long-term health risks and adverse outcomes for the affected offspring, including weight gain, obesity, and obesity-related cardio-metabolic complications [20,108]. Of note, gestational exposure to an obesogenic

diet – especially when high in fat and sugar – appears to predispose the offspring to severe weight gain and hypertriglyceridemia, as well as to the development of hepatic inflammation and fibrosis, when exposed to a similar diet later in life [108]. Interestingly, the combined effect of prenatal and postnatal obesogenic diets appears more than additive regarding hepatic fat accumulation [108].

Exposure to the intrauterine environment associated with maternal obesity is considered to have profound and lasting effects on the metabolic health of the offspring, irrespective of genetic predisposition and postnatal influences [109,110]. Human observational data and animal model studies collectively demonstrate the role of fetal programming in chronic disease risk. Indeed, offspring exposed to maternal obesity have a higher risk of developing obesity, T2DM, CVD, and MAFLD later in life [109,110]. This is also reflected in the results of a large cohort analysis based on a database of pregnancy data (the Aberdeen Maternity and Neonatal Databank) linked to national death/morbidity records (1,323,275 person years of follow-up), which revealed a 35% increased mortality, primarily from CVD causes, in such offspring [109]. Animal studies further support these associations by showing that maternal obesity in various species consistently programs cardio-metabolic diseases in the offspring, exacerbating the impact of diet-induced obesity in adulthood [111,112]. Additionally, animal studies have shown that maternal obesity influences the development of a dysmetabolic and MAFLD phenotype, which is highly dependent on the early postnatal period and may involve changes in hypothalamic appetite signaling due to maternal breast milk and neonatal adipose tissue-derived leptin [113].

A link between maternal obesity and MAFLD in the offspring has also been documented in longitudinal studies, suggesting that perinatal obesity or exposure to an obesogenic diet can predispose to MAFLD later in life [114]. For example, data from the Western Australian Pregnancy (Raine) Cohort study demonstrated an association of maternal pre-pregnancy obesity with a substantially increased risk for MAFLD in adolescents, independently of a Western dietary pattern at 17 years of age [115]. Canadian data by Soullane *et al.* [116] also demonstrated that offspring exposed to maternal obesity have an increased risk of developing MAFLD during childhood. Similar associations were observed in UK and USA studies, where elevated maternal pre-pregnancy BMI was independently linked to a higher risk of MAFLD in the exposed offspring [117,118]. Notably, a UK prospective pregnancy cohort study reported an adjusted odds ratio of 2.72 for ultrasound-diagnosed hepatic steatosis in the offspring (at a mean age of 17.8 years) of mothers with increased maternal pre-pregnancy BMI, which increased to 6.74 in the presence of maternal diabetes or glycosuria and was not mediated by the offspring's concurrent adiposity or birth weight [117]. In accord with these findings, the data from a prospective cohort study of 254 mother-child pairs in Colorado showed that maternal pre-pregnancy obesity was significantly associated with increased adolescent the hepatic fat fraction as assessed by MRI [118]. Finally, data based on biopsy-verified MAFLD from the ESPRESSO cohort study in Sweden also

support this association between maternal obesity and future MAFLD development in the exposed offspring [119]. Severe MAFLD (fibrosis or cirrhosis) was more common in the offspring of mothers with overweightness/obesity, independently of socio-economic and metabolic parameters, highlighting the role of maternal obesity as an independent risk factor for MAFLD in the offspring [119]. This feed-forward cycle emerges where maternal obesity and MAFLD during pregnancy fuel the development of obesity and MAFLD in the exposed offspring from an early age, thus leading to more women of childbearing age already having these problems when becoming pregnant.

## 5. Expert opinion

Advancements in research linking maternal obesity and MAFLD in pregnancy can profoundly impact real-world outcomes in antenatal care, given the increasing global prevalence of these conditions and their significant adverse effects on both mothers and offspring. Understanding the complex underlying pathophysiology – particularly the pathways and mediators linking adipose tissue dysfunction, insulin resistance, and hepatic inflammation and fibrosis – can enhance the sensitivity and specificity of diagnostic algorithms and lead to more effective treatments for MAFLD.

Pregnancy can indeed exacerbate MAFLD due to the metabolic and hormonal changes that occur during this period. Most women likely had MAFLD before pregnancy, particularly in relationship to obesity, which becomes more noticeable and is detected during pregnancy because of the closer routine follow-up during antenatal care. The postpartum period can see some improvement in MAFLD symptoms as the metabolic demands and hormonal levels stabilize, but this varies among individuals. Long-term management and follow-up are crucial to address the underlying metabolic dysfunctions that may persist beyond pregnancy.

Currently, improvements are needed in noninvasive diagnostic methods and personalized treatment strategies for MAFLD. Technological advancements, particularly in imaging and biomarker analysis, could enhance early detection and management of MAFLD in pregnancy. However, the integration of these advances into clinical practice may be delayed by economic constraints, healthcare policies, and the need for further validation of emerging diagnostic methods and treatments, especially in the context of pregnancy.

The development of universally accepted diagnostic criteria and safe, effective treatment modalities for pregnant women should be a primary focus of future clinical research. Large-scale, long-term studies are essential to establish evidence-based guidelines for managing MAFLD in pregnancy, which could significantly improve maternal and fetal health outcomes. Routine early identification of MAFLD during pregnancy could also prompt early screening for GDM, since GDM risk increases with the severity of MAFLD even after adjusting for age and other known risk factors.

Considering MAFLD assessment as part of pre-conception family planning could be beneficial. Although direct evidence for this specific recommendation is limited, existing literature indicates that 60–90% of adults with obesity have MAFLD. This

high prevalence supports the need for pre-pregnancy discussions and interventions to identify and manage MAFLD, potentially improving maternal and fetal outcomes.

Furthermore, MAFLD may increase the risk for the development and progression of several cardio-metabolic conditions, such as T2DM, cardiovascular disease, and pre-eclampsia. Therefore, MAFLD could be considered both a marker and a mediator of metabolic dysfunction, highlighting the need for targeted interventions to mitigate these risks.

Despite the increasing global incidence of MAFLD and its associated morbidity and mortality, specific drugs for steatohepatitis are now being developed/approved. Current clinical guidelines recommend lifestyle changes, including exercise and diet modifications, as the primary approach to managing MAFLD. When these interventions are insufficient for the non-pregnant population, options include bariatric surgery or pharmacotherapy (primarily for weight loss) to address underlying metabolic complications. Emerging pharmaceutical strategies aim to enhance metabolic function, reduce steatosis, decrease inflammation, and halt or reverse fibrosis progression. However, they are currently recommended to address coexisting metabolic complications such as obesity, T2DM, dyslipidemia, and hypertension. In pregnant women, drug treatment remains cautious due to safety concerns, with metformin and insulin being the primary approved drugs for managing GDM. GLP-1 receptor agonists have shown promise in improving metabolic parameters and reducing liver fat in non-pregnant patients, but their use is contraindicated in pregnancy. In pregnant women with obesity, avoiding excessive weight gain during pregnancy, preventing GDM, and controlling hyperglycemia are key strategies to combat the risks of maternal obesity and MAFLD for both the mother and the offspring. These strategies may also help break the apparent feed-forward cycle between obesity and MAFLD in young women of reproductive age, thereby reducing the increasing prevalence of maternal obesity and MAFLD during pregnancy.

Particularly promising is research on the axis between the liver, gut, and adipose tissue, as well as the role of gut microbiota dysregulation in MAFLD pathogenesis. In the next five to ten years, progress in this field is likely to offer a better understanding of MAFLD and its impact on maternal and fetal/offspring health. Consequently, routine practice may shift from a generalized approach to more personalized management strategies, incorporating individualized algorithms with genetic, multi-biomarker, and gut microbiota profiling to guide prevention, early diagnosis, and treatment.

Such personalized management could lead to a decreased incidence of MAFLD and its adverse outcomes during pregnancy and later in life, thus limiting the feed-forward cycle that appears to further fuel the transmission of cardio-metabolic disorders from affected mothers to their offspring. Developing universally accepted diagnostic criteria, as well as safe and effective treatment modalities for pregnant women, should remain a focus of future clinical research to support these advancements.

Overall, addressing the challenges and seizing the opportunities in this research area could significantly improve antenatal care and long-term health outcomes for both mothers and their children.

## 6. Conclusion

Maternal obesity and MAFLD during pregnancy are significant health concerns in antenatal care due to their increasing global prevalence and substantial adverse effects on both mothers and offspring. MAFLD, often under-recognized during pregnancy, is associated with an elevated risk of complications such as GDM, pre-eclampsia, and long-term cardio-metabolic diseases in the offspring. Current clinical guidelines emphasize lifestyle modifications as the primary management strategy, with cautious pharmacotherapy to address coexisting metabolic conditions due to safety concerns during pregnancy. Emerging treatments and diagnostic advancements show promise, but require further validation and integration into clinical practice.

The pathophysiology of MAFLD in pregnancy involves complex interactions between insulin resistance, adipokine dysregulation, and chronic low-grade inflammation, combined with normal pregnancy-related hormonal and metabolic changes. Research into the gut-liver axis and the role of gut microbiota offers new paths for understanding and managing MAFLD.

Future research should focus on developing noninvasive diagnostic methods and personalized treatment strategies, incorporating genetic and biomarker profiling. Early identification and management of MAFLD, potentially starting with pre-conception family planning, could mitigate risks and improve outcomes for both mothers and their children. Establishing universally accepted diagnostic criteria and safe treatment modalities for pregnant women is essential to advancing clinical care. By addressing these challenges, antenatal care could be significantly enhanced, breaking the cycle of metabolic dysfunction transmission across generations.

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## Author contributions

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## References

1. WHO. Obesity And Overweight. 2021.
2. Nightingale H, Mnatzaganian G, Hooker L, et al. The effect of motivational interviewing and/or cognitive behaviour therapy techniques on gestational weight gain – a systematic review and meta-analysis. *BMC Public Health*. 2023;23(1):626. doi: [10.1186/s12889-023-15446-9](https://doi.org/10.1186/s12889-023-15446-9)
3. Rogozińska E, Zamora J, Marlin N, et al. Gestational weight gain outside the institute of medicine recommendations and adverse pregnancy outcomes: analysis using individual participant data from randomised trials. *Bmc Pregnancy Childbirth*. 2019;19(1):322. doi: [10.1186/s12884-019-2472-7](https://doi.org/10.1186/s12884-019-2472-7)
4. Rasmussen KM, Yaktine AL. Institute of M, National Research Council Committee to Reexamine IOMPWG. The National Academies Collection: Reports funded by National Institutes of Health. *Weight Gain During Pregnancy: Reexamining the Guidelines*. 2009. p. 2–3.
5. Chen C, Xu X, Yan Y, et al. Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS One*. 2018;13(8):e0202183. doi: [10.1371/journal.pone.0202183](https://doi.org/10.1371/journal.pone.0202183)
6. Goldstein RF, Abell SK, Ranasinha S, et al. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. *JAMA*. 2017 Jun 6;317(21):2207–2225. doi: [10.1001/jama.2017.3635](https://doi.org/10.1001/jama.2017.3635)
7. Kominiaek M, Saade G, Mele L, et al. Association between gestational weight gain and perinatal outcomes. *Obstet & Gynecol Obstetrics And Gynecology (New York 1953)*. 2018;132(4):875–881. doi: [10.1097/AOG.0000000000002854](https://doi.org/10.1097/AOG.0000000000002854)
8. Najafi F, Hasani J, Izadi N, et al. The effect of prepregnancy body mass index on the risk of gestational diabetes mellitus: a systematic review and dose-response meta-analysis. *Obesity Rev*. 2019;20(3):472–486. doi: [10.1111/obr.12803](https://doi.org/10.1111/obr.12803)
9. Carrasco-Wong I, Moller A, Giachini FR, et al. Placental structure in gestational diabetes mellitus. *Biochim Biophys Acta Mol Basis Dis*. 2020 Feb 1;1866(2):165535. doi: [10.1016/j.bbadis.2019.165535](https://doi.org/10.1016/j.bbadis.2019.165535)
10. Moradi Y. The relationship between body mass index and pre-eclampsia: a systematic review and meta-analysis. *Int J Reprod Biomed (Yazd)*. 2022;20(12):1051–1052. doi: [10.18502/ijrm.v20i12.12568](https://doi.org/10.18502/ijrm.v20i12.12568)
11. He X-J, Dai R-X, Hu C-L. Maternal prepregnancy overweight and obesity and the risk of preeclampsia: a meta-analysis of cohort studies. *Obes Research & Clinical Practice*. 2020;14(1):27–33. doi: [10.1016/j.orcp.2020.01.004](https://doi.org/10.1016/j.orcp.2020.01.004)
12. Torloni MR, Betrán AP, Daher S, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. *J Matern-Fetal Neonatal Med*. 2009;22(11):957–970. doi: [10.3109/14767050903042561](https://doi.org/10.3109/14767050903042561)
13. Liu L, Ma Y, Wang N, et al. Maternal body mass index and risk of neonatal adverse outcomes in China: a systematic review and meta-analysis. *Bmc Pregnancy Childbirth*. 2019;19(1):105. doi: [10.1186/s12884-019-2249-z](https://doi.org/10.1186/s12884-019-2249-z)
14. Saadia Z. Association between maternal obesity and cesarean delivery complications. *Cureus*. 2020;12(3):e7163. doi: [10.7759/cureus.7163](https://doi.org/10.7759/cureus.7163)
15. Chu SY, Kim SY, Schmid CH, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. *Obesity Rev*. 2007;8(5):385–394. doi: [10.1111/j.1467-789X.2007.00397.x](https://doi.org/10.1111/j.1467-789X.2007.00397.x)

16. Castaneda C, Marsden K, Maxwell T, et al. Prevalence of maternal obesity at delivery and association with maternal and neonatal outcomes. *J Matern Fetal Neonatal Med.* 2022 Dec;35(25):8544–8551. doi: [10.1080/14767058.2021.1988563](https://doi.org/10.1080/14767058.2021.1988563)
17. Metsälä J, Stach-Lempinen B, Gissler M, et al. Risk of pregnancy complications in relation to maternal prepregnancy body mass index: population-based study from Finland 2006–10. *Paediatric Perinatal Epidemiol.* 2016 Jan;30(1):28–37. doi: [10.1111/ppe.12248](https://doi.org/10.1111/ppe.12248)
18. Scheidl TB, Brightwell AL, Easson SH, et al. Maternal obesity and programming of metabolic syndrome in the offspring: searching for mechanisms in the adipocyte progenitor pool. *BMC Med.* 2023 Feb 13;21(1):50. doi: [10.1186/s12916-023-02730-z](https://doi.org/10.1186/s12916-023-02730-z)
19. Dodd JM, Deussen AR, Mitchell M, et al. Maternal overweight and obesity during pregnancy: strategies to improve outcomes for women, babies, and children. *Expert Rev Endocrinol Metab.* 2022 Jul;17(4):343–349. doi: [10.1080/17446651.2022.2094366](https://doi.org/10.1080/17446651.2022.2094366)
20. Matuszak O, Banach W, Pogorzala B, et al. The long-term effect of maternal obesity on the cardiovascular health of the offspring-systematic review. *Curr Probl Cardiol.* 2024 Jan;49(1 Pt B):102062. doi: [10.1016/j.cpcardiol.2023.102062](https://doi.org/10.1016/j.cpcardiol.2023.102062)
21. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol.* 2023 Dec;79(6):1542–1556. doi: [10.1016/j.jhep.2023.06.003](https://doi.org/10.1016/j.jhep.2023.06.003)
22. Chan KE, Koh TJL, Tang ASP, et al. Global prevalence and clinical characteristics of metabolic associated fatty liver disease. A meta-analysis and systematic review of 10,739,607 individuals. *J Clin Endocrinol Metab.* 2022;107(9):2691–2700. doi: [10.1210/clinem/dgac321](https://doi.org/10.1210/clinem/dgac321)
23. Murag S, Ahmed A, Kim D. Recent epidemiology of nonalcoholic fatty liver disease. *Gut Liver.* 2021 Mar 15;15(2):206–216. doi: [10.5009/gnl20127](https://doi.org/10.5009/gnl20127)
24. Younossi ZM, Koenig AB, Abdelatif D, et al. 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](https://doi.org/10.1002/hep.28431)
25. Azzaroli F, Mazzella G, Marchesini G, et al. Fatty liver in pregnancy: a narrative review of two distinct conditions. *Expert Rev Gastroenterol Hepatol.* 2020 Feb;14(2):127–135. doi: [10.1080/17474124.2020.1715210](https://doi.org/10.1080/17474124.2020.1715210)
26. Younossi ZM. Non-alcoholic fatty liver disease – a global public health perspective. *J Hepatol.* 2019;70(3):531–544. doi: [10.1016/j.jhep.2018.10.033](https://doi.org/10.1016/j.jhep.2018.10.033)
27. Kubihal S, Gupta Y, Shalimar, et al. Prevalence of non-alcoholic fatty liver disease and factors associated with it in Indian women with a history of gestational diabetes mellitus. *J Of Diabetes Invest.* 2021 May;12(5):877–885. doi: [10.1111/jdi.13411](https://doi.org/10.1111/jdi.13411)
28. Mazzotti A, Caletti MT, Sasdelli AS, et al. Pathophysiology of non-alcoholic fatty liver disease: lifestyle-gut-gene interaction. *Dig Dis.* 2016;34(Suppl 1):3–10. doi: [10.1159/000447275](https://doi.org/10.1159/000447275)
29. Sarkar M, Grab J, Dodge JL, et al. Non-alcoholic fatty liver disease in pregnancy is associated with adverse maternal and perinatal outcomes. *J Hepatol.* 2020 Sep;73(3):516–522. doi: [10.1016/j.jhep.2020.03.049](https://doi.org/10.1016/j.jhep.2020.03.049)
30. Poon LC, McIntyre HD, Hyett JA, et al. The first-trimester of pregnancy – a window of opportunity for prediction and prevention of pregnancy complications and future life. *Diabetes Res Clin Pract.* 2018;145:20–30. doi: [10.1016/j.diabres.2018.05.002](https://doi.org/10.1016/j.diabres.2018.05.002)
31. Parretti S, Caroli A, Torlone E. Nutrition and metabolic adaptations in physiological and complicated pregnancy: focus on obesity and gestational diabetes. *Front Endocrinol.* 2020;11:611929. doi: [10.3389/fendo.2020.611929](https://doi.org/10.3389/fendo.2020.611929)
32. Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr.* 2000 May;71(5 Suppl):1256s–1261s. doi: [10.1093/ajcn/71.5.1256s](https://doi.org/10.1093/ajcn/71.5.1256s)
33. Armistead B, Johnson E, VanderKamp R, et al. Placental regulation of energy homeostasis during human pregnancy. *Endocrinology.* 2020 Jul 1;161(7). doi: [10.1210/endo/bqaa076](https://doi.org/10.1210/endo/bqaa076)
34. Lain K, Catalano P. Metabolic changes in pregnancy. *Clin Obstet Gynecol.* 2007;50(4):938–948. doi: [10.1097/GRF.0b013e31815a5494](https://doi.org/10.1097/GRF.0b013e31815a5494)
35. Zeng Z, Liu F, Li S. Metabolic adaptations in pregnancy. *Ann Nutr Metab.* 2017;70(1):59–65. doi: [10.1159/000459633](https://doi.org/10.1159/000459633)
36. Kampmann U, Knorr S, Fuglsang J, et al. Determinants of maternal insulin resistance during pregnancy: an updated overview. *J Diabetes Res.* 2019;2019:5320156. doi: [10.1155/2019/5320156](https://doi.org/10.1155/2019/5320156)
37. Catalano PM. Obesity, insulin resistance, and pregnancy outcome. *Reproduction.* 2010;140(3):365–371. doi: [10.1530/REP-10-0088](https://doi.org/10.1530/REP-10-0088)
38. Kalhan S, Rossi K, Gruca L, et al. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Investig.* 1997;100(7):1775–1781. doi: [10.1172/JCI119704](https://doi.org/10.1172/JCI119704)
39. Herrera E, Ortega-Senovilla H. Lipid metabolism during pregnancy and its implications for fetal growth. *Curr Pharm Biotechnol.* 2014;15(1):24–31. doi: [10.2174/1389201015666140330192345](https://doi.org/10.2174/1389201015666140330192345)
40. Catalano PM, Tyzbir ED, Wolfe RR, et al. Longitudinal changes in basal hepatic glucose production and suppression during insulin infusion in normal pregnant women. *Am J Obstet Gynecol.* 1992;167(4):913–919. doi: [10.1016/S0002-9378\(12\)80011-1](https://doi.org/10.1016/S0002-9378(12)80011-1)
41. Kelly AC, Powell TL, Jansson T. Placental function in maternal obesity. *Clin Sci (Lond).* 2020 Apr 30;134(8):961–984. doi: [10.1042/CS20190266](https://doi.org/10.1042/CS20190266)
42. Maltepe E, Fisher SJ. Placenta: the forgotten organ. *Annu Rev Cell Dev Biol.* 2015;31(1):523–552. doi: [10.1146/annurev-cellbio-100814-125620](https://doi.org/10.1146/annurev-cellbio-100814-125620)
43. Newbern D, Freemark M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes.* 2011 Dec;18(6):409–416. doi: [10.1097/MED.0b013e32834c800d](https://doi.org/10.1097/MED.0b013e32834c800d)
44. Cowett RM, Farrag HM. Selected principles of perinatal–neonatal glucose metabolism. Netherlands: Operating Company Elsevier Ltd; 2004. p. 37–47.
45. Baumann MU, Deborde S, Illsley NP. Placental glucose transfer and fetal growth. *Endocrine.* 2002;19(1):13–22. doi: [10.1385/ENDO:19:1:13](https://doi.org/10.1385/ENDO:19:1:13)
46. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental growth and metabolism. *Biochimica et biophysica acta molecular basis of disease. Biochim Biophys Acta (BBA) – Mol Basis Dis.* 2020;1866(2):165359. doi: [10.1016/j.bbadis.2018.12.010](https://doi.org/10.1016/j.bbadis.2018.12.010)
47. Sibiak R, Jankowski M, Gutaj P, et al. Placental lactogen as a marker of maternal obesity, diabetes, and fetal growth abnormalities: current knowledge and clinical perspectives. *J Clin Med.* 2020 Apr 16;9(4):1142. doi: [10.3390/jcm9041142](https://doi.org/10.3390/jcm9041142)
48. Sakurai Y, Kubota N, Yamauchi T, et al. Role of insulin resistance in MAFLD. *Int J Mol Sci.* 2021 Apr 16;22(8):4156. doi: [10.3390/ijms22084156](https://doi.org/10.3390/ijms22084156)
49. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta.* 2015 Jul;36(7):709–715. doi: [10.1016/j.placenta.2015.04.006](https://doi.org/10.1016/j.placenta.2015.04.006)
50. Kyrou I, Randeve HS, Tsigos C, et al. Clinical problems caused by obesity. In: Feingold K, Anawalt B, Blackman M, et al., Eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000–2023, MDText.com, Inc.; 2000.
51. Francisco V, Sanz MJ, Real JT, et al. Adipokines in non-alcoholic fatty liver disease: are we on the road toward new biomarkers and therapeutic targets? *Biology (Basel).* 2022 Aug 19;11(8):1237. doi: [10.3390/biology11081237](https://doi.org/10.3390/biology11081237)
52. Jiménez-Cortegana C, García-Galey A, Tami M, et al. Role of leptin in non-alcoholic fatty liver disease. *Biomedicines.* 2021;9(7):762. doi: [10.3390/biomedicines9070762](https://doi.org/10.3390/biomedicines9070762)
53. Flessa CM, Nasiri-Ansari N, Kyrou I, et al. Genetic and diet-induced animal models for non-alcoholic fatty liver disease (NAFLD) research. *Int J Mol Sci.* 2022 Dec 13;23(24):15791. doi: [10.3390/ijms232415791](https://doi.org/10.3390/ijms232415791)
54. Valenti L, Bugianesi E, Pajvani U, et al. Nonalcoholic fatty liver disease: cause or consequence of type 2 diabetes? *Liver Int.* 2016;36(11):1563–1579. doi: [10.1111/liv.13185](https://doi.org/10.1111/liv.13185)
55. Fouda S, Vennikandam MM, Pappachan JM, et al. 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](https://doi.org/10.14218/JCTH.2022.00052)
56. 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):1259. doi: [10.3390/cells8101259](https://doi.org/10.3390/cells8101259)

57. Flessa CM, Kyrou I, Nasiri-Ansari N, et al. Endoplasmic reticulum stress in nonalcoholic (metabolic associated) fatty liver disease (NAFLD/MAFLD). *J Cell Biochem*. 2022 Oct;123(10):1585–1606. doi: [10.1002/jcb.30247](https://doi.org/10.1002/jcb.30247)
58. Flessa CM, Kyrou I, Nasiri-Ansari N, et al. Endoplasmic reticulum stress and autophagy in the pathogenesis of non-alcoholic fatty liver disease (NAFLD): current evidence and perspectives. *Curr Obes Rep*. 2021 Jun;10(2):134–161. doi: [10.1007/s13679-021-00431-3](https://doi.org/10.1007/s13679-021-00431-3)
59. Kim TH, Hong D-G, Yang YM. Hepatokines and non-alcoholic fatty liver disease: linking liver pathophysiology to metabolism. *Biomedicines*. 2021;9(12):1903. doi: [10.3390/biomedicines9121903](https://doi.org/10.3390/biomedicines9121903)
60. Kolodziejczyk AA, Zheng D, Shibolet O, et al. The role of the microbiome in NAFLD and NASH. *EMBO Mol Med*. 2019 Feb;11(2). doi: [10.15252/emmm.201809302](https://doi.org/10.15252/emmm.201809302)
61. Wang JS, Liu JC. Intestinal microbiota in the treatment of metabolically associated fatty liver disease. *World J Clin Cases*. 2022 Nov 6;10(31):11240–11251. doi: [10.12998/wjcc.v10.i31.11240](https://doi.org/10.12998/wjcc.v10.i31.11240)
62. Kim JC, Jeon JY, Yang WS, et al. Combined amelioration of ginsenoside (Rg1, Rb1, and Rg3)-enriched Korean Red Ginseng and probiotic lactobacillus on non-alcoholic fatty liver disease. *Curr Pharm Biotechnol*. 2019;20(3):222–231. doi: [10.2174/1389201020666190311143554](https://doi.org/10.2174/1389201020666190311143554)
63. Loguercio C, Federico A, Tuccillo C, et al. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol*. 2005 Jul;39(6):540–543. doi: [10.1097/01.mcg.0000165671.25272.0f](https://doi.org/10.1097/01.mcg.0000165671.25272.0f)
64. Liu L, Li P, Liu Y, et al. Efficacy of probiotics and synbiotics in patients with nonalcoholic fatty liver disease: a meta-analysis. *Dig Dis Sci*. 2019 Dec;64(12):3402–3412. doi: [10.1007/s10620-019-05699-z](https://doi.org/10.1007/s10620-019-05699-z)
65. Yin X, Guo X, Liu Z, et al. Advances in the diagnosis and treatment of non-alcoholic fatty liver disease. *Int J Mol Sci*. 2023 Feb 2;24(3):2844. doi: [10.3390/ijms24032844](https://doi.org/10.3390/ijms24032844)
66. Papatheodoridi M, Cholongitas E. Diagnosis of non-alcoholic fatty liver disease (NAFLD): current concepts. *Curr Pharm Dis*. 2018;24(38):4574–4586. doi: [10.2174/1381612825666190117102111](https://doi.org/10.2174/1381612825666190117102111)
67. Henry L, Eberly KE, Shah D, et al. Noninvasive tests used in risk stratification of patients with nonalcoholic fatty liver disease. *Clin Liver Dis*. 2023 May;27(2):373–395. doi: [10.1016/j.cld.2023.01.022](https://doi.org/10.1016/j.cld.2023.01.022)
68. Stauffer K, Halilbasic E, Spindelboeck W, et al. Evaluation and comparison of six noninvasive tests for prediction of significant or advanced fibrosis in nonalcoholic fatty liver disease. *United Eur Gastroenterol J*. 2019 Oct;7(8):1113–1123. doi: [10.1177/2050640619865133](https://doi.org/10.1177/2050640619865133)
69. Kechagias S, Ekstedt M, Simonsson C, et al. Non-invasive diagnosis and staging of non-alcoholic fatty liver disease. *Hormones (Athens)*. 2022 Sep;21(3):349–368. doi: [10.1007/s42000-022-00377-8](https://doi.org/10.1007/s42000-022-00377-8)
70. Kahn HS. The “lipid accumulation product” performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovasc Disord*. 2005 Sep 8;5(1):26. doi: [10.1186/1471-2261-5-26](https://doi.org/10.1186/1471-2261-5-26)
71. Kyrou I, Panagiotakos DB, Kouli GM, et al. Lipid accumulation product in relation to 10-year cardiovascular disease incidence in Caucasian adults: the ATTICA study. *Atherosclerosis*. 2018 Dec;279:10–16. doi: [10.1016/j.atherosclerosis.2018.10.015](https://doi.org/10.1016/j.atherosclerosis.2018.10.015)
72. Ebrahimi M, Seyedi SA, Nabipoorashrafi SA, et al. Lipid accumulation product (LAP) index for the diagnosis of nonalcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. *Lipids Health Dis*. 2023 Mar 15;22(1):41. doi: [10.1186/s12944-023-01802-6](https://doi.org/10.1186/s12944-023-01802-6)
73. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006 Nov 2;6(1):33. doi: [10.1186/1471-230X-6-33](https://doi.org/10.1186/1471-230X-6-33)
74. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterol*. 2009 Sep;137(3):865–872. doi: [10.1053/j.gastro.2009.06.005](https://doi.org/10.1053/j.gastro.2009.06.005)
75. Koralegedara IS, Warnasekara JN, Rathnayake A, et al. Fatty liver index is a valid predictor of non-alcoholic fatty liver disease (NAFLD) in pregnancy. *BMJ Open Gastroenterol*. 2022 Jun;9(1):e000913. doi: [10.1136/bmjgast-2022-000913](https://doi.org/10.1136/bmjgast-2022-000913)
76. Bannaga AS, Metzger J, Kyrou I, et al. Discovery, validation and sequencing of urinary peptides for diagnosis of liver fibrosis-A multicentre study. *EBioMedicine*. 2020 Dec;62:103083. doi: [10.1016/j.ebiom.2020.103083](https://doi.org/10.1016/j.ebiom.2020.103083)
77. Jang W, Song JS. Non-invasive imaging methods to evaluate non-alcoholic fatty liver disease with fat quantification: a review. *Diagnostics (Basel)*. 2023 May 25;13(11):1852. doi: [10.3390/diagnostics13111852](https://doi.org/10.3390/diagnostics13111852)
78. Zeng KY, Bao WY, Wang YH, et al. Non-invasive evaluation of liver steatosis with imaging modalities: new techniques and applications. *World J Gastroenterol*. 2023 May 7;29(17):2534–2550. doi: [10.3748/wjg.v29.i17.2534](https://doi.org/10.3748/wjg.v29.i17.2534)
79. Theel W, Boxma-de Klerk BM, Dirksmeier-Harincck F, et al. Evaluation of nonalcoholic fatty liver disease (NAFLD) in severe obesity using noninvasive tests and imaging techniques. *Obes Rev*. 2022 Aug;23(8):e13481. doi: [10.1111/obr.13481](https://doi.org/10.1111/obr.13481)
80. Nogami A, Yoneda M, Iwaki M, et al. Non-invasive imaging biomarkers for liver steatosis in non-alcoholic fatty liver disease: present and future. *Clin Mol Hepatol*. 2023 Feb;29(Suppl):S123–s135. doi: [10.3350/cmh.2022.0357](https://doi.org/10.3350/cmh.2022.0357)
81. Lao TT. Implications of abnormal liver function in pregnancy and non-alcoholic fatty liver disease. *Best Pract Res Clin Obstet Gynaecol*. 2020 Oct;68:2–11. doi: [10.1016/j.bpobgyn.2020.02.011](https://doi.org/10.1016/j.bpobgyn.2020.02.011)
82. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. *J Hepatol*. 2016 Apr;64(4):933–945. doi: [10.1016/j.jhep.2015.11.030](https://doi.org/10.1016/j.jhep.2015.11.030)
83. Dajti E, Bruni A, Barbara G, et al. Diagnostic approach to elevated liver function tests during pregnancy: a pragmatic narrative review. *J Pers Med*. 2023 Sep 16;13(9):1388. doi: [10.3390/jpm13091388](https://doi.org/10.3390/jpm13091388)
84. Elefsiniotis IS, Tsoumakas K, Kapritsou M, et al. Liver function tests in viremic and nonviremic chronic hepatitis B virus-infected pregnant women: importance of alanine aminotransferase/sodium ratio. *Gastroenterol Nurs*. 2013 Nov;36(6):422–428. doi: [10.1097/SGA.0000000000000004](https://doi.org/10.1097/SGA.0000000000000004)
85. Mei-Dan E, Wiznitzer A, Sergienko R, et al. Prediction of preeclampsia: liver function tests during the first 20 gestational weeks. *J Matern Fetal Neonatal Med*. 2013 Feb;26(3):250–253. doi: [10.3109/14767058.2012.733771](https://doi.org/10.3109/14767058.2012.733771)
86. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol*. 2013 Nov;209(5):456.e1–7. doi: [10.1016/j.ajog.2013.07.006](https://doi.org/10.1016/j.ajog.2013.07.006)
87. Liu G, Shang X, Yuan B, et al. Acute fatty liver of pregnancy: analysis on the diagnosis and treatment of 15 cases. *J Reprod Med*. 2016 May;61(5–6):282–286.
88. Morisco F, Bruno R, Bugianesi E. AISF position paper on liver disease and pregnancy. *Dig Liver Dis*. 2016 Feb;48(2):120–137. doi: [10.1016/j.dld.2015.11.004](https://doi.org/10.1016/j.dld.2015.11.004)
89. Flemming JA, Mullin M, Lu J, et al. Outcomes of pregnant women with cirrhosis and their infants in a population-based study. *Gastroenterology*. 2020 Nov;159(5):1752–1762.e10. doi: [10.1053/j.gastro.2020.07.052](https://doi.org/10.1053/j.gastro.2020.07.052)
90. 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 Feb;20(2):e315–e318. doi: [10.1016/j.cgh.2021.01.022](https://doi.org/10.1016/j.cgh.2021.01.022)
91. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007 Sep;46(3):922–938. doi: [10.1002/hep.21907](https://doi.org/10.1002/hep.21907)
92. Bertot LC, Jeffrey GP, Wallace M, et al. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. *Hepatol Commun*. 2017 Feb;1(1):53–60. doi: [10.1002/hep4.1018](https://doi.org/10.1002/hep4.1018)
93. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American association for the

- study of liver diseases. *Hepatology*. 2017 Jan;65(1):310–335. doi: [10.1002/hep.28906](https://doi.org/10.1002/hep.28906)
94. Galle PR, Forner A, Llovet JM. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018 Jul;69(1):182–236. doi: [10.1016/j.jhep.2018.03.019](https://doi.org/10.1016/j.jhep.2018.03.019)
95. Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterol*. 2011 Oct;141(4):1249–1253. doi: [10.1053/j.gastro.2011.06.061](https://doi.org/10.1053/j.gastro.2011.06.061)
96. Platner MH, Ackerman CM, Howland RE, et al. Severe maternal morbidity and mortality during delivery hospitalization of class I, II, III, and super obese women. *Am J Obstet Gynecol*. 2021 Sep;3(5):100420. doi: [10.1016/j.ajogmf.2021.100420](https://doi.org/10.1016/j.ajogmf.2021.100420)
97. Durst JK, Tuuli MG, Stout MJ, et al. Degree of obesity at delivery and risk of preeclampsia with severe features. *Am J Obstet Gynecol*. 2016 May;214(5):651.e1–5. doi: [10.1016/j.ajog.2015.11.024](https://doi.org/10.1016/j.ajog.2015.11.024)
98. Crane JM, Murphy P, Burrage L, et al. Maternal and perinatal outcomes of extreme obesity in pregnancy. *J Obstet Gynaecol Can*. 2013 Jul;35(7):606–611. doi: [10.1016/S1701-2163\(15\)30879-3](https://doi.org/10.1016/S1701-2163(15)30879-3)
99. Sarkar M, Brady CW, Fleckenstein J, et al. Reproductive health and liver disease: practice guidance by the American association for the study of liver diseases. *Hepatology*. 2021 Jan;73(1):318–365. doi: [10.1002/hep.31559](https://doi.org/10.1002/hep.31559)
100. Hagström H, Höjjer J, Ludvigsson JF, et al. Adverse outcomes of pregnancy in women with non-alcoholic fatty liver disease. *Liver Int*. 2016 Feb;36(2):268–274. doi: [10.1111/liv.12902](https://doi.org/10.1111/liv.12902)
101. Lee SM, Jung YM, Choi ES, et al. Metabolic dysfunction-associated fatty liver disease and subsequent development of adverse pregnancy outcomes. *Clin Gastroenterol Hepatol*. 2022 Nov;20(11):2542–2550.e8. doi: [10.1016/j.cgh.2021.11.007](https://doi.org/10.1016/j.cgh.2021.11.007)
102. El Jamaly H, Eslick GD, Weltman M. Systematic review with meta-analysis: non-alcoholic fatty liver disease and the association with pregnancy outcomes. *Clin Mol Hepatol*. 2022 Jan;28(1):52–66. doi: [10.3350/cmh.2021.0205](https://doi.org/10.3350/cmh.2021.0205)
103. 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 Sep;7(3):305–311. doi: [10.5114/ceh.2021.109228](https://doi.org/10.5114/ceh.2021.109228)
104. Koralegedara IS, Warnasekara JN, Dayaratne KG, et al. Non-alcoholic fatty liver disease (NAFLD): a significant predictor of gestational diabetes mellitus (GDM) and early pregnancy miscarriages – prospective study in rajarata pregnancy cohort (RaPco). *BMJ Open Gastroenterol*. 2022 Feb;9(1):e000831. doi: [10.1136/bmjgast-2021-000831](https://doi.org/10.1136/bmjgast-2021-000831)
105. Jung YM, Lee SM, Hong S, et al. The risk of pregnancy-associated hypertension in women with nonalcoholic fatty liver disease. *Liver Int*. 2020 Oct;40(10):2417–2426. doi: [10.1111/liv.14563](https://doi.org/10.1111/liv.14563)
106. Herath RP, Siriwardana SR, Ekanayake CD, et al. 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](https://doi.org/10.1371/journal.pone.0215326)
107. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014 Dec 2;161(11):819–826. doi: [10.7326/M14-1884](https://doi.org/10.7326/M14-1884)
108. Vos MB. Furthering the understanding of maternal obesity in non-alcoholic fatty liver disease. *Hepatology*. 2013 Jul;58(1):4–5. doi: [10.1002/hep.26389](https://doi.org/10.1002/hep.26389)
109. Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ*. 2013 Aug 13;347(aug13 1):f4539. doi: [10.1136/bmj.f4539](https://doi.org/10.1136/bmj.f4539)
110. Glastras SJ, Chen H, Pollock CA, et al. Maternal obesity increases the risk of metabolic disease and impacts renal health in offspring. *Biosci Rep*. 2018 Apr 27;38(2). doi: [10.1042/BSR20180050](https://doi.org/10.1042/BSR20180050)
111. Lagisz M, Blair H, Kenyon P, et al. Little appetite for obesity: meta-analysis of the effects of maternal obesogenic diets on offspring food intake and body mass in rodents. *Int J Obes (Lond)*. 2015 Dec;39(12):1669–1678. doi: [10.1038/ijo.2015.160](https://doi.org/10.1038/ijo.2015.160)
112. Mouralidarane A, Soeda J, Visconti-Pugmire C, et al. Maternal obesity programs offspring nonalcoholic fatty liver disease by innate immune dysfunction in mice. *Hepatology*. 2013 Jul;58(1):128–138. doi: [10.1002/hep.26248](https://doi.org/10.1002/hep.26248)
113. Oben JA, Mouralidarane A, Samuelsson AM, et al. Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice. *J Hepatol*. 2010 Jun;52(6):913–920. doi: [10.1016/j.jhep.2009.12.042](https://doi.org/10.1016/j.jhep.2009.12.042)
114. Thompson MD. Developmental programming of NAFLD by parental obesity. *Hepatol Commun*. 2020 Oct;4(10):1392–1403. doi: [10.1002/hep4.1578](https://doi.org/10.1002/hep4.1578)
115. Ayonrinde OT, Oddy WH, Adams LA, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. *J Hepatol*. 2017 Sep;67(3):568–576. doi: [10.1016/j.jhep.2017.03.029](https://doi.org/10.1016/j.jhep.2017.03.029)
116. Soullane S, Willems P, Lee GE, et al. Early life programming of nonalcoholic fatty liver disease in children. *Early Hum Dev*. 2022 May;168:105578. doi: [10.1016/j.earlhumdev.2022.105578](https://doi.org/10.1016/j.earlhumdev.2022.105578)
117. Patel S, Lawlor DA, Callaway M, et al. Association of maternal diabetes/glycosuria and pre-pregnancy body mass index with offspring indicators of non-alcoholic fatty liver disease. *BMC Pediatr*. 2016 Mar 31;16(1):47. doi: [10.1186/s12887-016-0585-y](https://doi.org/10.1186/s12887-016-0585-y)
118. Bellatorre A, Scherzinger A, Stamm E, et al. Fetal overnutrition and adolescent hepatic fat fraction: the exploring perinatal outcomes in children study. *J Pediatr*. 2018 Jan;192:165–170.e1. doi: [10.1016/j.jpeds.2017.09.008](https://doi.org/10.1016/j.jpeds.2017.09.008)
119. Hagström H, Simon TG, Roelstraete B, et al. Maternal obesity increases the risk and severity of NAFLD in offspring. *J Hepatol*. 2021 Nov;75(5):1042–1048. doi: [10.1016/j.jhep.2021.06.045](https://doi.org/10.1016/j.jhep.2021.06.045)