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Review

Impact of Gut–Brain Axis on Hepatobiliary Diseases in Fetal Programming

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Abstract: The hepatobiliary system is vital for the biotransformation and disposition of endogenous molecules. Any impairment in the normal functioning of the hepatobiliary system leads to a spectrum of hepatobiliary diseases (HBDs), such as liver cirrhosis, fatty liver, biliary dyskinesia, gallbladder cancer, etc. Especially in pregnancy, HBD may result in increased maternal and fetal morbidity and mortality. Maternal HBD is a burden to the fetus's growth, complicates fetal development, and risks the mother's life. In fetal programming, the maternal mechanism is significantly disturbed by multiple factors (especially diet) that influence the development of the fetus and increase the frequency of metabolic diseases later in life. Additionally, maternal under-nutrition or over-nutrition (especially in high-fat, high-carbohydrate, or protein-rich diets) lead to dysregulation in gut hormones (CCK, GLP-1, etc.), microbiota metabolite production (SCFA, LPS, TMA, etc.), neurotransmitters (POMC, NPY, etc.), and hepatobiliary signaling (insulin resistance, TNF-a, SREBPs, etc.), which significantly impact fetal programming. Recently, biotherapeutics have provided a new horizon for treating HBD during fetal programming to save the lives of the mother and fetus. This review focuses on how maternal impaired hepatobiliary metabolic signaling leads to disease transmission to the fetus mediated through the gut–brain axis.

Keywords: hepatobiliary diseases; gut axis; brain axis; microbiota metabolites; fetal programming

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1. Introduction

The hepatobiliary system is a key target organ that has a critical role in the biotransformation and deposition of endogenous molecules. In the initial phase of fetal programming, the concentration of estrogen and progesterone abruptly increases in pregnant women, which may alter the hepatobiliary system (bile production slows down) and result in hepatobiliary disease (HBD) [1–3]. HBD in fetal programming is highly considerable and might even be fatal for the mother and the fetus. Some HBDs may have been present before the pregnancy, or may have occurred coincidentally with the pregnancy such as gallstones, cirrhosis, or hepatitis [4]. HBD found exclusively in pregnant women includes diseases like intrahepatic cholestasis of pregnancy (ICP), low platelets (HELLP) syndrome, hemolysis, acute fatty liver of pregnancy (AFLP), and elevated liver enzymes. Alcoholic HBD during fetal programming has a greater risk of small-for-gestational-age fetuses and preterm birth outcomes. Nonalcoholic fatty liver disease (NAFLD) is an immensely prevalent disease, frequently known as the hepatic manifestation of metabolic problems and is also associated with the risk of birth outcome [5,6].

Maternal HBD has a huge impact on fetal programming and future metabolic diseases of the fetus. A British epidemiologist, David Barker, coined the term "Fetal program-

ming", which is the phenomenon of the exposure of a neonate or fetus to an abnormal maternal environment during the fetal developmental period. He studied the association between low birth weight and the high risk of developing chronic disease in adulthood [7]. Barker's hypothesis suggested that any impairment associated with the hepatobiliary system may result in low birth weight and increase the risk of diseases such as hypertension, diabetes, atherosclerosis, and dyslipidemia in late childhood or adulthood [8]. Despite not knowing the exact mechanism of fetal programming, the link between intrauterine stress and its detrimental effects on offspring like the occurrence of diseases such as asthma, dermatitis, and eczema has been confirmed, along with an increase in the risk of infections and diseases such as cancer (notably testicular cancer, hepatic cancer, and lymphoma), cardiovascular disease, and metabolic dysfunction [7,9].

The gastrointestinal and neuronal axis in HBD during fetal programming represents a dysregulation that occurs coincidentally with the mother and affects the fetus's life (Figure 1). Dysregulation in gastrointestinal hormones (CCK, GLP-1, etc.), microbiota metabolite production (SCFA, LPS, TMA, etc.), neurotransmitters (POMC, NPY, etc.), and hepatobiliary signaling (insulin resistance, TNF-a, SREBPs, etc.) significantly impact together fetal programming [10–12]. HBD in connection with gastrointestinal and neuronal dysregulation in pregnancy is not well specified, but certain abnormalities may represent the molecular mechanism of the gastrointestinal–neuronal axis in HBD during pregnancy. This review will summarize the role of the gastrointestinal and neuronal axis impacting hepatobiliary pathophysiology in mother and birth outcomes, highlighting areas for potential mechanisms and birth outcomes for preventive intervention.

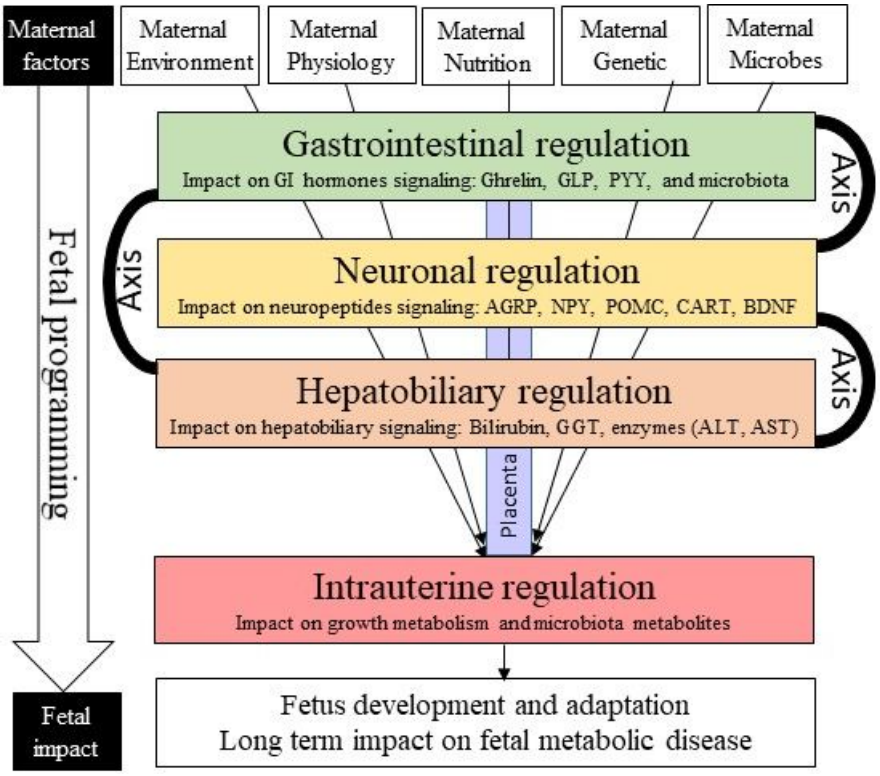

Figure 1. Systematic representation of fetal development and effects of different material factors.

2. Gut Impact on Hepatobiliary Disease in Fetal Programming

In the initial stage, which is the first trimester (6–8 weeks), of fetal programming, vomiting and nausea are very common and are usually self-controlled. Around 80% of pregnant women experience at least one episode of vomiting and suffered from nausea [13]. The exact cause of vomiting and nausea during fetal programming is unclear but gastrointestinal dysfunction might be responsible. Hyperemesis gravidarum is a severe form of nausea and vomiting that affects 1 in 200 pregnant women [14]. Multiple pregnancies,

gastrointestinal diseases, psychiatric illnesses, and preexisting diabetes are associated risk factors with hyperemesis gravidarum [15]. Hormone fluctuations in pregnancy like rising levels of estrogen and progesterone might also be responsible for hyperemesis gravidarum during pregnancy. While miscarriages, stillbirths, preterm births, growth retardation, low birth weight, preeclampsia, peripheral neuropathy, and mortality are birth outcomes of hyperemesis gravidarum [16,17]. Abnormal hepatic biochemistry is observed in half of the women hospitalized with hyperemesis [18]. Excessive vomiting is a sign of gastroenteritis usually caused by an infection of microbes, chemical toxins, or drugs. In addition, the consumption of exotic seafood or mushrooms during fetal programming may produce chemical toxins and cause gastroenteritis. Constipation is another gastrointestinal culprit that around 40% of pregnant women experience during the early stages of pregnancy [19]. Constipation increases the chances of abdominal pain through dehydration, electrolyte imbalance, or poor fiber intake and, as a consequence, nausea. Reflux esophagitis (symptoms are heartburn) is experienced by around 80% of women during fetal programming, mostly in the third trimester [20]. Reflux esophagitis is the most prevalent gastrointestinal disease globally and esophageal adenocarcinoma is an important factor that increases the risk of HBD [21]. Obstetric cholestasis has been linked to increased stillbirth, premature labor (12–44%) and fetal distress, the fetal passage of meconium, and fatal intracranial hemorrhage [22]. In addition, esophageal adenocarcinoma development (Barrett's esophagus) is strongly associated with prolonged gastroesophageal reflux of gastric and bile acids [23]. Gallstone pancreatitis is also observed during fetal programming, usually biliary pancreatitis in the third trimester, and alcohol consumption, hypertriglyceridemia, and hyperparathyroidism are risk factors for gallstone pancreatitis development [24,25].

Maternal nutrition plays a crucial role in fetal programming, influencing the development of hepatobiliary diseases in the mother. Unhealthy dietary habits during pregnancy heighten the risk of these conditions. Moreover, nonalcoholic fatty liver disease (NAFLD), a component of metabolic syndrome, is on the rise, alongside increasing obesity and diabetes rates. While traditionally linked to excessive caloric intake and sedentary lifestyles, recent research implicates diets high in sugar, such as sucrose and high-fructose corn syrup (HFCS), in elevating the risk of NAFLD and nonalcoholic steatohepatitis (NASH). Fructose metabolism, particularly by fructokinase C, contributes to hepatic fat accumulation by promoting lipogenesis and hindering fat oxidation, while alterations in gut permeability and the microbiome further exacerbate susceptibility to NAFLD and NASH. Early clinical studies suggest that reducing sugary beverage consumption and overall fructose intake, particularly from added sugars, may mitigate hepatic fat accumulation. Larger-scale trials are needed to confirm whether minimizing sugar/HFCS intake or targeting uric acid production could effectively combat NAFLD and its complications [26]. Hyperemesis gravidarum due to malnutrition (protein and calories) and vitamin deficiency (especially B6 and B12) results in significantly low birth weight infants [27]. Under-nutrition during fetal programming results in the restriction of intrauterine growth, effecting the growth and functioning of other organs [28]. In a study, maternal food restriction during the final stage of pregnancy and a balanced diet during lactation elevated the concentration of homocysteine by disrupting the one-carbon metabolism in the liver. A study showed that male offspring are more susceptible to acquiring metabolic diseases later in their life as a result of fetal programming [29]. Another study found that feed restriction during pregnancy and lactation has a detrimental effect on the growth of the hepatic system and the metabolism of lipids [30]. A maternal diet low in protein fails to adequately support the growth of pancreatic cells, resulting in smaller cell sizes, inadequate formation of islets, and reduced insulin production. This deficiency may contribute to the development of insulin resistance during fetal programming. Thus, the underdevelopment may result in pancreatic β-cell and mass reduction of the hepatic cell that results in the development of insulin resistance, diabetes, and cardiovascular disease in the fetus [31,32]. Most dietary fats, such as saturated and unsaturated fatty acids, sterols, and triacylglycerol, are absorbed in the small intestine. After the intake of food, GLP-1 is deposited in the small intestine,

which promotes glucose uptake by stimulating the secretion of insulin by pancreatic β-cell. The consumption of a high-fat diet disrupts this signaling process and induces insulin resistance and deterioration of pancreatic β-cell function in adult offspring [33,34].

Gastrointestinal microbiota is significantly affected by dietary consumption during fetal programming. Microbial infections are the major cause of gastroenteritis, which is sometimes much more severe during fetal programming, leading to stillbirth (fetal loss) [35]. Microbes like norovirus and rotavirus are common viruses, and *Clostridium*, *Escherichia*, *Salmonella*, *Shigella*, *Staphylococci*, *Giardia*, and *Cryptosporidium* are common bacteria for gastrointestinal enteric infection. Local ischemia resulting from intestinal mucosal injury can cause the translocation of bacteria from the gastrointestinal tract to the circulatory system, contributing to the formation of sepsis through septic multiple organ failure syndromes (including hepatic system) by their endotoxins [36]. Dysbiosis of gastrointestinal microbiota might influence vaginal microbiota dynamics during fetal programming and affect birth outcomes [37]. Table 1 describes HBD and related microbes.

Table 1. Microbiome of specific hepatobiliary disease.

Hepatobiliary Disease	Microbiome	References
Alcoholic liver disease	*Bacteroidetes*, *Lactobacillus*, *Candida*, *Enterobacteriaceae*	[38,39]
Cirrhosis	*Veillonella*, *Streptococcus*, *Neisseria*, *Gemella*	[40,41]
Nonalcoholic fatty liver disease	*Bacteroides vulgatus*, *Ruminococcus*, *Escherichia coli*, *Prevotella*	[42,43]
Hepatocellular carcinoma	*Escherichia coli*, *Helicobacter* species	[44,45]

3. Brain Impact on Hepatobiliary Diseases in Fetal Programming

The brain plays an important part in and during fetal programming. Neurological problems related to liver disease may affect the peripheral nervous system, CNS, or both. Pregnant women undergo a drastic change, starting from embryo implant until infant birth, including the structure and function of the pregnant woman's brain. The rising level of hormones during pregnancy influences the brain's neurotransmitter activity, which causes certain emotions. The findings from the study conducted by Oatridge et al. (2002), revealed that both healthy individuals and those diagnosed with preeclampsia exhibited a decrease in brain size during pregnancy, reaching its peak at term and returning to normal levels within 6 months after delivery [46]. Additionally, ventricular size showed a corresponding increase during pregnancy followed by a decrease post-delivery. Notably, individuals with preeclampsia demonstrated significantly smaller brain sizes ($p = 0.05$) compared with their healthy counterparts, both before and after delivery. The study by Oatridge et al. highlighted a consistent pattern of brain size fluctuations during the perinatal period, although the precise mechanisms and physiological implications of these observations remain speculative at this time [46]. A systematic review of 146 case studies involving 177 HG patients found that the depletion of thiamine due to excessive vomiting can lead to Wernicke's encephalopathy, a degenerative brain disorder [47]. MRI reveals symmetrical lesions surrounding the aqueduct and the fourth ventricle of the mother, which is associated with severe nausea in others and accounts for around 40% of fetus' death. Pseudotumor cerebri syndrome is a neurological condition in which the pressure increases inside the skull, which leads to chronic inflammation of the hepatic system. Certain medications that contain vitamin A increase the risk of developing pseudotumor cerebri. Headaches and migraines are also often suffered by pregnant women. Migraines are much more complicated than just a headache and are often associated with multiple disorders, like nonalcoholic fatty liver disease and irritable bowel syndrome [48,49]. In hepatic encephalopathy, the neurotransmission in the brain is disrupted as a result of extreme hepatocellular failure. Nutritional imbalance in the mother during fetal programming significantly impacts the brain function of pregnant women. Nutrients such as omega-3 (O-3) polyunsaturated fatty acids (PUFAs) and omega-6 (n-6) are essential for the normal

development of the brain [50]. Among the different fatty acids in the brain, ubiquitin C-terminal hydrolase L1 (UCH-L1) is among the most abundant protein, accounting for 1–5% of total neuron protein. Essential nutrients like omega-3 (O-3) polyunsaturated fatty acids (PUFAs) and omega-6 (n-6) are vital for normal brain development [50]. Among the various fatty acids found in the brain, ubiquitin C-terminal hydrolase L1 (UCH-L1) stands out as one of the most abundant proteins, constituting 1–5% of the total neuron protein content. Food restriction (50%) of pregnant mouse's offspring brain at 3 weeks old shows a dramatic change in the concentration of UCH-L1 compared with the control [51]. Food restriction during pregnancy dysregulates the food intake-related neurotransmitter (anorexigenic POMC/orexigenic NPY/MC4R) expression [52]. A low-protein diet can be favorable for developing hypertension in adult life [53]. Neurological syndromes commonly occur with HBD, and may increase complications that may be induced by various factors like alcohol. Consumption of alcohol during pregnancy is not only bad for the hepatic system but can also result in neurological disorders, which interfere with the action of gamma-aminobutyric acid, glutamate, and other neurotransmitters [54].

4. Molecular Mechanism of Gut–Brain Axis on Hepatobiliary Disease in Fetal Programming

A growing body of evidence supports the notion that epigenetic changes, including histone modifications, DNA methylation, and microRNA (miRNA) expression, play a crucial role in fetal metabolic programming by influencing chromatin structure. These epigenetic mechanisms provide a molecular framework through which the fetus adapts to its intrauterine environment, responding to both nutritional deficiencies and excesses. The interplay between these epigenetic modifications orchestrates profound changes in gene expression patterns, leading to alterations in tissue-specific methylated cytosine residues, dynamics of histone acetylation/deacetylation, and regulation of cell differentiation and stem cell pluripotency. Moreover, emerging evidence suggests that the hypothalamus and liver may exhibit distinct epigenetic responses to adverse nutritional conditions during fetal development, highlighting the complexity of fetal metabolic programming [55]. The molecular mechanism of fetal programming of fetal development and its long-term health consequences will be discussed briefly. Two mechanisms mediate epigenetic effects. The first is DNA methylation and the second is histone modification, which affects the fetal programming of postnatal disease susceptibility and genomic imprinting. Nutritional insult during fetal programming may leave a permanent "footprint" throughout the life of the fetus and some of the effects may be gender-specific. The micronutrient is one of the important uteroplacental factors transferring from the mother to the fetus; thus, insufficient nutrient supply may alter DNA methylation, histone acetylation, and one-carbon metabolism in IUGR [56]. One-carbon unit metabolism depends on micronutrients like B vitamins (folate, B-12, and B-6), lysine, and serine, which generate SAM (universal methyl donor) for DNA methylation and histone modification [57]. Epigenetic changes and altered microbiomes may undergo vertical transmission from mother to offspring. The high-fat diet enhances the concentration of intestinal epithelial histone deacetylase 3 (HDAC3), and SCFA butyrate supplementation reduces HDAC3 activity [58]. A study by Lee et al. (2020) revealed that maternal food restriction during pregnancy affects the expression of hypothalamic appetite regulators (anorexigenic POMC/orexigenic NPY/MC4R) via epigenetic change [59].

5. Hepatobiliary Disease in Fetal Programming and Birth Outcome

Hepatobiliary diseases include a wide range of conditions with diverse etiology, prevalence, and clinical indices [60]. Studies suggest that the maternal diet affects the dysregulation in hepatic metabolism through changes in taurine levels and HNF4A methylation and might lead to offspring developing Type 2 diabetes and nonalcoholic fatty liver disease later in life. Malnutrition and over-nutrition is highly unhealthy for the mother and the fetus and can lead to underweight and overweight fetuses, respectively,

and any change from the normal nutrition, be it under or over, might lead to metabolic disease risk (Figure 2). Almost 60% of children with biliary cysts diagnosed prenatally display liver function impairment and clinical symptoms, mainly due to bile obstruction. A recent systematic review showed that biliary atresia was present in 22% of fetuses diagnosed as having biliary cysts on prenatal ultrasound, and one of the key reasons was maternal malnutrition [61]. Intrahepatic cholestasis of pregnancy characterized by impaired transportation and sulfation of bile acids and decreased bile uptake can cause vasoconstriction of chorionic veins in the placenta, leading to premature deliveries, fetal bradycardia, and even fetal loss. An analysis of the birth cohort in Finland from 1985 to 1986 found that ICP has an impact on the metabolic health of adolescent offspring. The study found that male offspring of ICP patients had higher BMI and fasting insulin compared with the offspring of healthy pregnant women. They also found that female offspring of ICP patients had significantly larger hip and waist girth compared with offspring of healthy pregnant women [62]. Preeclampsia and eclampsia—hypertension-related liver diseases—can cause oligohydramnios, intrauterine growth retardation, preterm delivery, placental abruption, and loss of fetus. A study conducted in a tertiary care center in Turkey involving 350 pregnant women with preeclampsia found that 66.6% of the women gave birth prematurely. Among them, 10.6% of the babies were admitted to the neonatal intensive care unit [63]. Preeclampsia-induced fetal programming is believed to predispose offspring to a number of disorders and diseases. Abuiessa et al. (2020) found that preeclampsia-induced fetal programming exacerbates the manifestations of hypotension and autonomic disfunction in male offspring [64]. AFLP, a rare yet highly life-threatening disorder, can be deadly to the mother and can cause low gestational age and preterm delivery. Nelson et al. (2013) analyzed the data of pregnant patients at Parkland Hospital from 1975 to 2012 and identified 51 women with AFLP [65]. Among the identified patients, they identified two maternal deaths and seven stillbirths. Another study involving 142,450 pregnant women, among whom 18 were identified to have AFLP, Joueidi et al. (2020) found that, although AFLP can cause fatal complications in maternal health, it does not have a significant impact on the fetus other than low gestational age at delivery [66].

In prenatal screening, abdominal and pelvic masses are frequently detected and often manifest as cystic structures. However, pinpointing the exact origin and nature of these cystic masses can be challenging before birth. While prenatal MRI imaging can provide valuable insights in many cases, achieving a definitive diagnosis remains elusive in some instances. Postnatal sonography, coupled with other imaging modalities when necessary, plays a pivotal role in elucidating the cause and precise location of these cystic lesions. Sonography is preferred for its accessibility, safety, affordability, and ability to provide high-resolution images, making it the primary imaging tool for neonates. Prompt and accurate diagnosis is essential, as management strategies for these lesions range from conservative approaches to surgical interventions. This article aims to delineate the diverse diagnoses and characteristic sonographic features of neonatal abdominal and pelvic cystic lesions, aiding healthcare professionals in making accurate diagnostic assessments [60]. Hepatobiliary cysts have been linked to several unfavorable effects, including stomach pain, cyst rupture, and bile blockage symptoms such as cholestasis, cholangitis, and liver fibrosis. Prenatal ultrasound shows hepatobiliary cysts as hypoechoic or anechoic or spherical structures inside the liver parenchyma, with a possibility of interconnection with the biliary system [67]. The key outcome of accurate prenatal diagnosis of these anomalies lies in the differential diagnosis. For instance, hepatic cysts are usually considered benign with a low probability of postnatal symptoms and requirement for surgery. On the other hand, the biliary cysts might present with symptoms associated with cholestasis in the neonatal period, consequently necessitating prompt surgical intervention. Additionally, biliary cysts could be easily misdiagnosed as biliary atresia, which is a congenital anomaly categorized by agenesis of the bile ducts leading to cirrhosis, portal hypertension, and eventually liver failure if remaining undiagnosed or left untreated [68]. When cystic formation is seen in

the fetal liver, antenatal counseling becomes challenging because the evidence is scant and primarily obtained from small series. Furthermore, it is still unknown whether congenital biliary malformations such as biliary atresia, in which a cystic structure is found in the fetal liver, actually exist. It is crucial to give parenting advice based on multiple rather than lone research, as limited research that is vulnerable to publication bias may not be sufficient. Therefore, further research is needed to understand the diagnosis, prognosis, and treatment of neonatal hepatobiliary diseases.

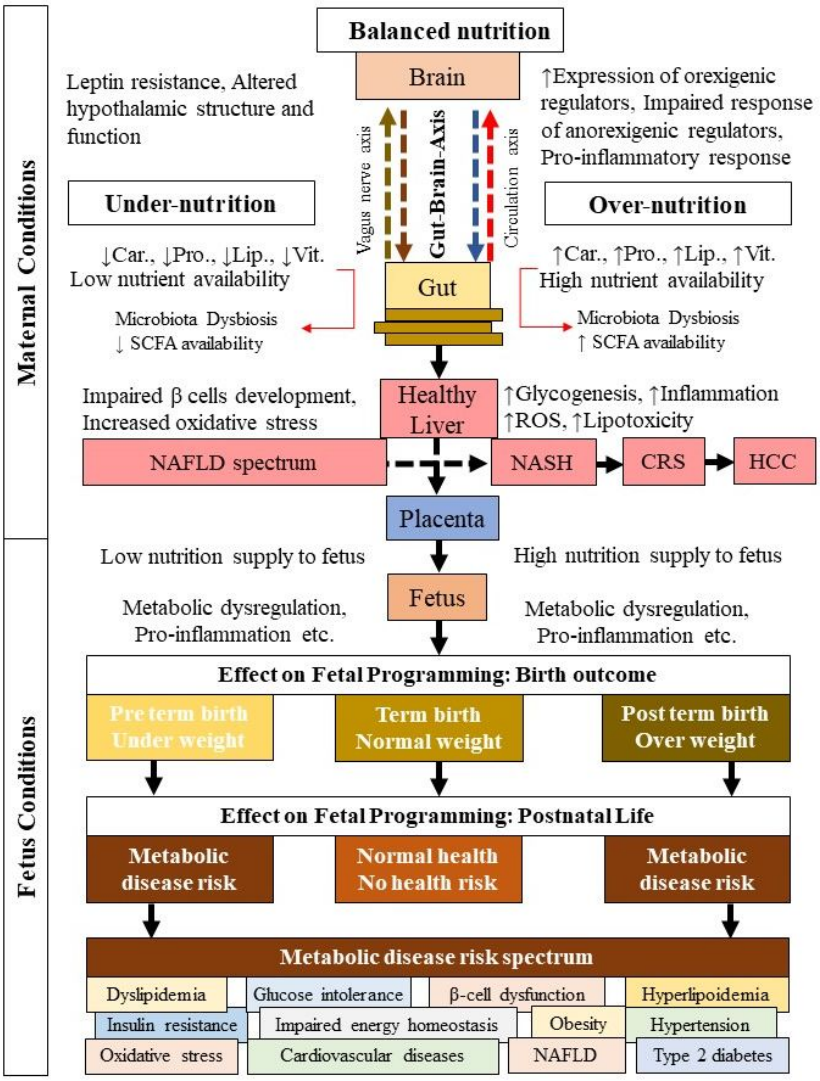

Figure 2. Systematic representation of gut-brain axis in fetal programming. Car: carbohydrates; Pro: proteins, Lip: lipids; Vit: vitamins; SCFA: short chain fatty acids; ROS: relative oxidative stress; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; CRS: cirrhosis; HCC: hepatocellular carcinoma.

6. Therapeutic Measure for Hepatobiliary Disease during Fetal Programming

Immediate therapeutics can lead to a better outcome for both mother and infant. Considering the health of the mother and fetus, various diagnoses like ultrasound, CT scan, MRI scan, hepatic biopsy, and biochemical analysis must be accounted for in the management of HBD during pregnancy. The laboratory findings on the hepatobiliary system may predict the birth outcome of the fetus. Most pregnant women are excessively cautious with anti-emetics during pregnancy, especially in the first trimester, unless vomiting is very severe, due to the fear of teratogenicity. Vitamin B_6 has no teratogenic effect and is given to pregnant women for controlling nausea and vomiting [69]. Corticosteroids are generally

considered safe drugs for nausea and vomiting; however, a meta-analysis revealed that they increase the risk of oral cleft development in the first trimester [70]. Adequate liquid consumption prevents dehydration, electrolyte disturbances, and weight loss and reduces the risk of hyperemesis gravidarum and constipation. Avoiding taking meals just before bedtime or eating late at night reduces the risk of gastro reflux or esophagitis. Bacterial translocation can be reduced by selective decontamination, which reduces the population of bacteria in the gut tract (viz. enterobacteria). Consumption of SCFA, Vit D, Vit A, zinc, cysteine, methionine, glutamine, tryptophan, arginine, and a glutamine-containing diet can prevent intestinal permeability [71–73]. Glutamine supplementation and maternal high-fiber diets have been found to improve gut integrity and decrease intestinal permeability in the mother and the offspring [71,72]. Pregnant women having a genetic history of hepatic damage, multifetal pregnancy, or chronic hepatitis C have a higher possibility of developing cholestasis during pregnancy (third trimester). Genetic testing can provide insights into the likelihood of passing a disorder to the fetus. Research indicates that dietary exposure in both animals and humans can result in heightened hepatobiliary dysregulation in mothers, increasing the risk of developing NAFLD/NASH later in life. Hepatic biochemical abnormalities can usually be improved by the intake of sufficient nutrients and avoiding consumption of exotic food to reduce the chance of toxic gastroenteritis. Switching from pharmacological therapy (viz. corticosteroid) to non-pharmacological therapy like meditation, acupressure, and emotional support will reduce HBD during fetal programming [74,75]. Shifting from a high-fat or high-carbohydrate diet to a high-fiber and low-fat diet can change the pathogenic gut microbiota (*Eubacterium*/*Clostridium*) population related to obesity and hepatic diseases [76]. In a recent study, You et al. (2016) observed that retinoid metabolism improves the accuracy of preterm birth prediction [77]. The recent trend of treatment with probiotic mixtures for constipation during pregnancy might be helpful [78] (Figure 2).

7. Biomedicines (Probiotics) in Hepatobiliary Disease during Pregnancy

Active microorganisms that are beneficial to health—called probiotics—have been used for the treatment of different diseases, including liver diseases, obesity, diabetes, etc. [79,80]. The administration of probiotics during pregnancy is found to be safe for the mother and the fetus [81,82], offering an attractive alternative for the treatment of various hepatobiliary diseases during pregnancy. Different probiotics have been found to improve the quality of life of pregnant women by improving various organ and system functions during pregnancy. For example, a study on the effect of the probiotic *Lactobacillus* in 32 obstetric patients found that the probiotic improved quality of life by decreasing the severity of nausea, vomiting, and constipation, which are common symptoms during pregnancy. It was believed that the probiotics produced free bile acids that facilitate better metabolism and intestinal motility [83]. Probiotic therapy is believed to be capable of modulating nutrient-sensing molecules in the placenta, restoring lipid dysmetabolism in the fetus, and mediating the short-chain fatty acid signaling pathway. The impact of probiotic *Lactobacillus reuteri* and sodium butyrate was tested on pregnant mice and was found to reduce fat in the liver and improved liver steatosis in the mother and in the offspring. The authors believed that *Lactobacillus reuteri* could be used as an adjuvant therapy in the treatment of NAFLD in pregnant women and as a de-programming strategy for NAFLD in the offspring of NAFLD patients [84]. Administration of the prebiotic oligofructose to pregnant mice with NAFLD also improved hepatic steatosis in both male and female offspring and lowered the probability of developing a more severe steatosis or NAFLD in offspring [85]. Treatment of ICP mice with the probiotic *Lactobacillus rhamnosus* GG was capable of reducing ICP-associated bile acid accumulation and liver injury. This was mediated by the activation of hepatic farnesoid X receptor (FXR) and upregulation of bile salt export pump (BSEP) [86]. Probiotics in combination with ursodeoxycholic acid were also found to be capable of reducing blood lipid level, liver inflammation, and hepatic cell damage and improved fatty liver in pregnant mice with cholestatic liver disease [87].

Oral administration of the probiotic *Lactobacillus plantarum* BJ0021 to pregnant rats exposed to the pesticide endosulfan was found to protect the liver and kidney cells against the toxicity of endosulfan and improved liver function. *L. plantarum* prevented the apoptosis of hepatic cells by scavenging and eliminating the free radicals, although the exact mechanism involved in the elimination of free radicals was not known [88].

Intake of probiotics like *Bifidobacterium longum*, *Bifidobacterium breve*, *Lactobacillus casei*, and *Lactobacillus acidophilus* reduced the activity of liver enzymes like alanine and aspartate aminotransferases in patients with NAFLD, which led to an improvement in symptoms [80]. However, probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* was found to have no significant effect on the levels of alanine and aspartate aminotransferases in healthy pregnant women [89]. Administration of probiotic enteric-coated capsules in combination with ursodeoxycholic acid soft capsules to 82 ICP patients increased alkaline phosphatase (ALP) and γ-glutamyltransferase (γ-GT) enzyme levels and decreased blood ammonia (BA) levels. These effectively improved the liver function and intestinal flora of ICP patients [90]. Another probiotic, *L. rhamnosus* LRX01, was found to inhibit the expression of FXR in the ileum of pregnant ICP patients. This inhibition of FXR may improve intestinal immunity of the infant of an ICP patient by reducing the susceptibility to lipopolysaccharide (LPS) exposure [91].

Most studies regarding the effect of probiotics on liver diseases were conducted on nonpregnant individuals, making it hard to firmly conclude the benefits of probiotics for the treatment of hepatobiliary diseases in pregnant women. Also, it was still not clear whether the presence of certain probiotic strains in the gut was a "bad" disease driving force or a "good" self-regulation. As a result, the application of probiotics for the treatment of hepatobiliary diseases in pregnancy still needs further research and should be approached with caution.

8. Conclusions and Future Research Perspective

The successful management of HBD during pregnancy requires a multidisciplinary approach with fine collaboration between obstetricians, hepatologists, and internists to explore dynamic diagnostic and therapeutic aspects of these life-threatening diseases of mother and fetus. Further evaluation is needed to assess the efficacy and cost-effectiveness of various medications, including macrobiotic probiotic therapy, in the treatment of hepatobiliary diseases during fetal programming. Regarding future research perspective, various HBDs are still untouched, like whether maternal nutrition affects DNA methylation or alters histone modifications in the placenta, uterus, and fetus, fetal postnatal gut, brain, and hepatic tissues. Extreme attention is required for the detection of early signs and symptoms of gut–brain axis dysfunction and HBD during fetal programming. Furthermore, molecular studies are required for the clinical management of HBD in connection with the gut–brain axis.

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