

Review

Hepatobiliary Disorders in Pregnancy: A Comprehensive Clinical Review of Gallstone Disease, Intrahepatic Cholestasis, and Viral Hepatitis

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Abstract

Hepatobiliary disorders during pregnancy represent a significant cause of maternal and fetal morbidity, requiring careful differentiation between physiological adaptations of pregnancy and true hepatic pathology. This narrative review provides a comprehensive overview of three major hepatobiliary conditions encountered during pregnancy: gallstone disease, intrahepatic cholestasis of pregnancy (ICP), and viral hepatitis (HAV, HBV, HCV, HDV, and HEV). Pregnancy-induced hormonal and immunological changes influence disease pathogenesis, clinical presentation, diagnostic interpretation, and therapeutic decision-making. Gallstone disease remains the most common non-obstetric surgical condition in pregnancy, with contemporary evidence supporting timely laparoscopic intervention when indicated. ICP is characterized by pruritus and elevated serum bile acids and is associated with increased risks of preterm birth, fetal distress, and stillbirth, necessitating close surveillance and individualized delivery planning. Viral hepatitis poses unique challenges because of the potential for vertical transmission, maternal complications, and adverse neonatal outcomes. Universal antenatal screening for hepatitis B and C is increasingly recognized as a cornerstone of care. For HBV, maternal antiviral prophylaxis combined with neonatal immunoprophylaxis has reduced mother-to-child transmission to below 1%, whereas the role of direct-acting antivirals for HCV during pregnancy continues to evolve. HEV remains the most severe viral hepatitis in pregnancy, carrying disproportionately high maternal mortality in endemic regions. Across all conditions, multidisciplinary management involving hepatologists, gastroenterologists, obstetricians, maternal–fetal medicine specialists, surgeons, and neonatologists is essential to optimize outcomes. This review synthesizes current evidence, highlights pregnancy-specific diagnostic and therapeutic considerations, and identifies emerging areas of research that may further improve maternal and neonatal outcomes.



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1. Part I: Hepatobiliary Disorders in Pregnancy—Gallstone Disease

Hepatobiliary disorders during pregnancy present a unique and complex clinical challenge, requiring a balance between optimizing maternal health and ensuring fetal safety. Liver disease complicates approximately 3% of all pregnancies and remains a significant

cause of maternal and perinatal morbidity and mortality [1]. The clinical presentation of these disorders can range from asymptomatic biochemical abnormalities to fulminant hepatic failure.

A critical first step in evaluating a pregnant patient with suspected hepatobiliary disease is distinguishing between physiological changes in normal pregnancy and true pathology. During a normal pregnancy, several physiological adaptations occur that alter standard liver biochemical tests. For instance, serum alkaline phosphatase (ALP) levels can rise up to three to four times the upper limit of normal during the third trimester, primarily due to placental production and increased bone turnover [2]. Similarly, serum albumin levels typically decrease due to hemodilution, while alpha-fetoprotein and cholesterol levels increase. Conversely, serum aminotransferases (ALT and AST), bilirubin, and prothrombin time remain within normal non-pregnant limits; any elevation in these markers should prompt immediate clinical investigation [2].

Hepatobiliary disorders in this population can be broadly categorized into two groups: diseases unique to pregnancy (such as hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, preeclampsia-associated liver dysfunction, and acute fatty liver of pregnancy) and pre-existing or coincidental diseases that occur during pregnancy (such as viral hepatitis, autoimmune liver disease, and gallstone disease) [3].

Although gallstone disease, intrahepatic cholestasis of pregnancy, and viral hepatitis are pathophysiologically distinct entities, they are grouped together in this review because they share a common clinical thread: each requires the treating clinician to distinguish pregnancy-adapted physiology from true hepatobiliary pathology, and each carries direct implications for fetal as well as maternal wellbeing. In routine antenatal and acute-care practice, these three conditions are also the ones most commonly responsible for abnormal liver biochemistry or right-upper-quadrant symptoms in pregnant patients, so a single practical reference spanning surgical, medical, and infectious hepatobiliary disease is more useful at the point of care than three separate, narrowly focused reviews. This review is intended primarily for obstetricians, gastroenterologists, hepatologists, general and acute-care surgeons, and maternal-fetal medicine specialists who must make time-sensitive diagnostic and management decisions in this population.

1.1. Gallstone Disease: Cholelithiasis, Cholecystitis, and Cholangitis

Gallstone disease is one of the most common non-obstetric surgical conditions encountered during pregnancy. The physiological changes in pregnancy—specifically increased estrogen (which increases biliary cholesterol saturation) and increased progesterone (which decreases gallbladder motility and emptying)—create a highly lithogenic environment [4]. Consequently, new gallstones or biliary sludge develop in up to 12% of pregnancies, though the majority remain asymptomatic [4]. When symptomatic, the spectrum of gallstone disease ranges from uncomplicated biliary colic to severe complications such as acute cholecystitis, choledocholithiasis, ascending cholangitis, and gallstone pancreatitis. Beyond maternal morbidity, untreated or recurrent symptomatic gallstone disease is associated with fetal risks including preterm labor, and gallstone pancreatitis in particular carries a disproportionately high risk of fetal loss, which is a key driver of the shift toward earlier surgical intervention discussed below. Management strategies must be carefully tailored to the trimester of pregnancy and the severity of the presentation.

Symptoms mirror those in non-pregnant patients, including right upper quadrant (RUQ) or epigastric pain, nausea, vomiting, and Murphy's sign in cases of cholecystitis. However, the enlarging uterus can displace the abdominal organs, sometimes altering the classic location of pain in the later stages of pregnancy. Leukocytosis is a normal physiological finding in pregnancy (up to 12,000–16,000 cells/mcL), making it a less reliable marker

for infection [2]. Elevations in AST, ALT, bilirubin, and GGT suggest choledocholithiasis or cholangitis. As noted, ALP is naturally elevated in the third trimester and is not a reliable indicator of biliary obstruction. Transabdominal ultrasound is the gold standard and first-line imaging modality due to its high sensitivity for detecting gallstones and its complete safety for the fetus [5]. If ultrasound is inconclusive and choledocholithiasis is suspected, Magnetic Resonance Cholangiopancreatography (MRCP) without gadolinium contrast is the preferred second-line modality. Computed Tomography (CT) should generally be avoided due to ionizing radiation exposure to the fetus [5].

1.2. Management Across Trimesters

The management approach for symptomatic gallstone disease in pregnancy has shifted significantly over the past decade. Historically, conservative management was favored to delay surgery until the postpartum period. However, recent guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the American College of Obstetricians and Gynecologists (ACOG) advocate for early surgical intervention when indicated, as conservative management is associated with high rates of symptom recurrence, multiple hospital readmissions, and increased risks of severe complications (e.g., gallstone pancreatitis) which carry high fetal mortality rates [6].

1.2.1. First Trimester

Uncomplicated biliary colic is generally managed conservatively with intravenous hydration, antiemetics, and safe analgesics such as acetaminophen, to avoid surgical intervention during the period of fetal organogenesis, minimizing the risk of teratogenesis and spontaneous abortion [7]. If symptoms are severe, refractory, or complicated by cholecystitis, laparoscopic cholecystectomy can be performed; surgery should not be delayed if the mother's health is at risk.

1.2.2. Second Trimester

The second trimester is widely considered the safest period for surgical intervention. Organogenesis is complete, reducing teratogenic risks, and the uterus is not yet large enough to significantly obscure the surgical field [6]. Laparoscopic cholecystectomy is the treatment of choice for acute cholecystitis and recurrent biliary colic, with lower rates of preterm labor and fetal loss compared to surgery in the first or third trimesters [7].

1.2.3. Third Trimester

Laparoscopic cholecystectomy becomes technically challenging in the late third trimester due to the gravid uterus, which limits intra-abdominal working space and increases the risk of uterine injury during trocar placement. For uncomplicated biliary colic or mild cholecystitis, a trial of conservative management is often attempted to bridge the patient to the postpartum period [8]. If the patient fails conservative therapy or develops severe complications, surgery is still indicated. In some late-term cases, a percutaneous cholecystostomy tube may be placed by interventional radiology as a temporizing measure to decompress the infected gallbladder until postpartum surgery can be safely performed [8]. Prolonged conservative management in the third trimester is not without fetal risk: maternal sepsis from untreated cholecystitis or cholangitis can precipitate preterm labor, and continuous fetal monitoring is advised whenever a decompression procedure is undertaken late in pregnancy.

1.3. Management of Choledocholithiasis and Cholangitis

Choledocholithiasis and ascending cholangitis represent medical emergencies requiring prompt biliary decompression. Endoscopic Retrograde Cholangiopancreatography

(ERCP) is the procedure of choice for clearing the common bile duct and is considered safe during pregnancy when performed by experienced endoscopists [9]. To minimize fetal radiation exposure, ERCP should be performed with lead shielding for the maternal pelvis, minimized fluoroscopy time (or using radiation-free, wire-guided techniques), and avoidance of spot radiographs [9]. Following successful ERCP and sphincterotomy, a laparoscopic cholecystectomy should ideally be performed during the same admission (if in the first or second trimester) to prevent recurrent biliary events [9]. Untreated ascending cholangitis carries substantial fetal risk, as maternal sepsis and systemic inflammation are associated with preterm labor, fetal distress, and, in severe cases, fetal loss; this fetal risk is a central reason why biliary decompression should not be delayed regardless of gestational age.

1.4. Key Differences from Non-Pregnant Patients

Although the presentation of gallstone disease is broadly similar in pregnant and non-pregnant patients, several aspects of diagnostic interpretation and management differ in ways that are directly relevant to clinical decision-making. Table 1 summarizes the key differences between pregnant and non-pregnant patients with gallstone disease across biochemical interpretation, imaging strategy, and surgical timing, synthesizing the trimester- and modality-specific considerations discussed above (Table 1).

Table 1. Key diagnostic and management differences in gallstone disease: pregnant vs. non-pregnant patients.

Feature	Non-Pregnant Patient	Pregnant Patient
ALP Levels	Reliable marker for biliary obstruction.	Unreliable in 3rd trimester due to placental production.
WBC Count	Reliable marker for infection/inflammation.	Less reliable; physiological leukocytosis of pregnancy (up to 16,000 cells/mcL).
Imaging	CT scan frequently used in acute abdomen.	Ultrasound 1st line; MRCP without contrast 2nd line. CT avoided.
ERCP	Standard fluoroscopy used.	Requires lead shielding, minimal fluoroscopy, or radiation-free techniques.
Surgical Timing	Early cholecystectomy for acute cholecystitis.	Early surgery preferred; technically challenging in 3rd trimester. Temporizing cholecystostomy tube may be used.

2. Part II: Intrahepatic Cholestasis of Pregnancy

2.1. Introduction and Clinical Presentation

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis (OC), is a hepatic disorder occurring in the late second and early third trimesters of gestation [10]. Generalized, frequently intense pruritus is the predominant presenting symptom, usually manifesting after the 30th week of gestation. It primarily impacts the palms and soles and is often more severe at night. Cholestasis may also present with nausea, reduced appetite, fatigue, discomfort in the right upper quadrant, dark urine, and pale feces. Clinical jaundice, although infrequent, may manifest in roughly 14–25% of individuals, typically emerging between one to four weeks after the onset of pruritus [11].

2.2. Diagnosis

The diagnosis of ICP is typically based on the presence of pruritus in the third trimester and elevated levels of bile acids in the serum. Serum bile acid levels have 91% sensitivity and 93% specificity for ICP, with 10 µmol/L as the cut-off value [12]. The likelihood of fetal

complications escalates in cases of severe cholestasis with elevated serum bile acid levels typically exceeding 40 $\mu\text{mol/L}$ [10]. The severity is ascertained by bile acid concentrations, with values of 100 $\mu\text{mol/L}$ or greater linked to a markedly elevated risk of adverse fetal outcomes, including stillbirth [13]. Table 2 summarizes these serum bile acid thresholds and their corresponding clinical actions.

Table 2. Serum bile acid thresholds in ICP: diagnostic significance and clinical action.

Serum Bile Acid Level	Clinical Significance	Recommended Action
<10 $\mu\text{mol/L}$	Below diagnostic threshold for ICP.	ICP unlikely; seek alternative diagnosis.
≥ 10 $\mu\text{mol/L}$	Diagnostic for ICP (91% sensitivity, 93% specificity).	Initiate UDCA therapy; monitor closely.
>40 $\mu\text{mol/L}$	Severe ICP; elevated risk of adverse fetal outcomes.	Intensify monitoring; consider early delivery planning.
≥ 100 $\mu\text{mol/L}$	Markedly elevated risk of stillbirth.	Delivery by 35–36 weeks gestation recommended.

Liver enzymes are rarely elevated; serum alkaline phosphatase may be elevated physiologically. Elevated bilirubin may occur in 25% of cases but seldom surpasses 6 mg/dL [14]. Alternative etiologies of cholestasis—such as viral hepatitis, biliary obstruction, drug-induced hepatic damage, and autoimmune liver disease—must be ruled out by appropriate laboratory assessments and imaging techniques [15].

2.3. Management

Ursodeoxycholic acid (UDCA) is the preferred medication for managing ICP [16]. While the optimal initial dose is not definitively established, commencing at 300 mg twice daily is advisable, with the potential to escalate to 300 mg three times daily until delivery. Typically, maternal symptoms subside within approximately two weeks, and bile acid levels diminish by two to three weeks. If symptoms or bile acid levels do not improve, the dosage may be adjusted weekly or biweekly, up to a maximum of 21 mg/kg/day [17].

For patients refractory to UDCA, alternative agents such as rifampin, cholestyramine, and S-adenosyl-L-methionine are available [18]. Early planned delivery is recommended in severe cases to mitigate the risk of unexpected fetal demise. Elevated total bile acid concentrations exceeding 100 $\mu\text{mol/L}$ are significantly predictive of stillbirth in singleton pregnancies; hence, delivery by 35 to 36 weeks is recommended for these women [15]. The Royal College of Obstetricians and Gynaecologists (RCOG) advises induction of labor after 37 weeks, whereas the American College of Obstetricians and Gynecologists (ACOG) suggests delivery between 36 and 37 weeks [19].

2.4. Pregnancy-Specific Considerations

ICP is a reversible syndrome that often resolves within days post-delivery and may recur in future pregnancies. The primary concern is fetal threat, encompassing stillbirth, spontaneous preterm birth, and meconium-stained amniotic fluid, with risk escalating as bile acid levels increase [20]. Unlike cholestatic disease in non-pregnant individuals, management in ICP focuses on enhancing fetal outcomes via prompt delivery rather than extended pharmacological treatment. Vigilant antenatal surveillance and timely intervention remain the cornerstone of care.

3. Part III: Viral Hepatitis in Pregnancy

3.1. Introduction

Viral hepatitis is a global public health problem of considerable magnitude. Collectively, infections with the five recognized hepatotropic viruses—hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV)—account for an estimated 1.1 million deaths annually, with the vast majority attributable to the long-term complications of chronic HBV and HCV infection [21]. When these infections occur during pregnancy, the clinical and epidemiological consequences extend beyond the mother to encompass the developing fetus and neonate, often with lifelong implications.

Pregnancy represents a period of significant immunological adaptation. The partial suppression of cell-mediated immunity that facilitates maternal tolerance of the semi-allogeneic fetus also alters the natural history of certain viral infections. In the case of HBV, immune reactivation in the postpartum period can precipitate hepatic flares of considerable severity [22]. HEV infection during pregnancy, particularly with genotypes 1 and 2, is associated with fulminant hepatic failure and maternal mortality that substantially exceeds rates seen in non-pregnant adults [23]. These pregnancy-specific vulnerabilities underscore the need for a clear and systematic approach to diagnosis and management.

The burden of viral hepatitis in pregnancy is not distributed evenly across the globe. HBV remains endemic across sub-Saharan Africa and much of Asia, where vertical transmission from mother to child has historically been the predominant route of chronic infection acquisition [24,25]. HEV epidemics linked to genotypes 1 and 2 continue to affect pregnant women in South Asia and sub-Saharan Africa, contributing disproportionately to maternal mortality during outbreaks [26]. In high-income countries, HCV has emerged as an increasingly important concern in pregnancy, driven in part by the ongoing opioid epidemic and improved universal screening programs [27].

3.2. Methods

This narrative review, encompassing all three topics (gallstone disease, intrahepatic cholestasis of pregnancy, and viral hepatitis), was informed by a literature search conducted in December 2025 across three electronic databases: PubMed (MEDLINE), Embase, and the Cochrane Library, encompassing publications from January 2000 to December 2025. Search terms combined pregnancy-related vocabulary (“pregnancy,” “pregnant,” “gestation,” “perinatal,” “maternal-fetal”) with condition-specific terms for each of the three topics (“cholelithiasis,” “cholecystitis,” “choledocholithiasis,” “cholangitis” for Part I; “intrahepatic cholestasis,” “obstetric cholestasis,” “bile acids” for Part II; and “hepatitis A/B/C/D/E,” “HAV/HBV/HCV/HDV/HEV,” “vertical transmission,” “mother-to-child transmission” for Part III), combined using Boolean operators and adapted to the syntax of each database. A total of 482 records were identified across the three topics combined; after removal of duplicates and title/abstract screening by two authors independently, 90 articles were retained for full-text review and incorporated into the final narrative. Articles were included if they were published in English, involved pregnant or peripartum populations, and addressed clinical diagnosis, pathophysiology, antiviral or surgical management, pregnancy complications, vertical or mother-to-child transmission, or neonatal outcomes relevant to the three conditions under review. Case reports describing fewer than five patients, non-English-language publications, conference abstracts without a corresponding full-text article, and studies focused exclusively on non-pregnant populations were excluded. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, and current society guidelines (AASLD, ACOG, EASL, RCOG, APASL, SAGES, SMFM), with older or lower-quality evidence retained only where more recent or

higher-quality data were unavailable. Discrepancies in study selection were resolved by discussion among the author team. The review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA).

3.3. *Hepatitis A in Pregnancy*

3.3.1. Epidemiology

Hepatitis A virus is a single-stranded RNA virus transmitted primarily via the fecal–oral route. Although self-limiting, it can cause significant acute hepatitis with occasional progression to fulminant liver failure. In low-endemicity regions, susceptible pregnant women may encounter HAV during travel or outbreaks [28]. The global incidence of HAV has declined substantially following the introduction of effective vaccines, but sporadic outbreaks continue [29].

3.3.2. Diagnosis

The diagnosis of acute HAV infection is established by detection of HAV-specific IgM antibodies in serum, becoming positive within one to two weeks of symptom onset [30]. Liver function tests typically reveal markedly elevated ALT. In pregnancy, overlapping symptoms such as nausea, fatigue, and anorexia may delay diagnosis, necessitating a high index of clinical suspicion [30].

3.3.3. Management

There is no specific antiviral therapy for acute HAV infection; management is entirely supportive. The inactivated HAV vaccine is safe in pregnancy and is recommended for susceptible women at increased risk of exposure. Post-exposure prophylaxis with intramuscular human immunoglobulin is effective if administered within two weeks of exposure in unvaccinated pregnant women [29,31,32].

3.3.4. Pregnancy-Specific Considerations

Acute HAV infection during pregnancy is associated with an increased risk of preterm labor and premature rupture of membranes, particularly in the second or third trimester [29,31]. Vertical transmission is extremely rare, though peripartum fecal–oral transmission has been documented. Breastfeeding is generally safe as HAV is not excreted in clinically significant quantities in breast milk [31,32].

3.4. *Hepatitis B in Pregnancy*

3.4.1. Epidemiology

HBV is the most common cause of chronic viral hepatitis globally, affecting an estimated 257 million people. An estimated 0.5–5% of pregnant women worldwide are HBsAg-positive [33]. Without appropriate prophylaxis, the risk of mother-to-child transmission (MTCT) ranges from 10–40%, rising to over 90% in HBeAg-positive mothers with high viral loads, with a greater than 90% probability of chronicity in perinatally infected neonates [34]. Regional epidemiological surveillance remains essential for tracking progress toward elimination targets; for example, recent national surveillance data from China illustrate both continued declines in HBsAg seroprevalence among women of childbearing age and the persistent burden requiring sustained prophylaxis programs [25].

3.4.2. Diagnosis

Antenatal screening for HBV should be universal, offered at the first prenatal visit. All HBsAg-positive women should undergo further evaluation including HBeAg, anti-HBe, serum HBV DNA quantification, liver function tests, and assessment for cirrhosis [35]. HBV

DNA exceeding 200,000 IU/mL is the strongest independent predictor of immunoprophylaxis failure and perinatal transmission [36].

3.4.3. Management: Antiviral Prophylaxis

Current international guidelines from AASLD, APASL, and INASL recommend initiating antiviral prophylaxis in HBsAg-positive pregnant women with HBV DNA exceeding 200,000 IU/mL, typically at 24–28 weeks of gestation [24,37–39]. Tenofovir disoproxil fumarate (TDF) is the preferred agent, with randomized controlled trials demonstrating MTCT reduction to less than 1% when combined with neonatal immunoprophylaxis [40,41]. Tenofovir alafenamide (TAF) is a reasonable alternative when renal concerns exist [42–44]. Lamivudine should be reserved for settings where TDF is unavailable [45]. Interferon-based therapies are absolutely contraindicated in pregnancy [46].

3.4.4. Neonatal Immunoprophylaxis

The combined administration of hepatitis B immunoglobulin (HBIG) and the first dose of the HBV vaccine within twelve hours of birth reduces perinatal transmission by approximately 85–95% without antiviral prophylaxis, and to less than 1% when combined with maternal antiviral therapy [47–49]. The HBV vaccine series should be completed at one and six months. In preterm or low birth weight infants, dosing schedules should be individualized due to potentially attenuated immune responses [50].

3.4.5. Pregnancy-Specific Considerations

Chronic HBV infection is associated with increased risks of gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, preterm birth, and antepartum hemorrhage [51]. The postpartum hepatic flare requires close monitoring [22,52]. Breastfeeding does not meaningfully increase HBV transmission risk and should be encouraged in women receiving TDF or TAF [53]. Routine cesarean section for HBV alone is not justified [54]. Invasive prenatal procedures in women with high HBV viral load carry elevated transmission risk and should be approached with caution [55].

3.5. Hepatitis C in Pregnancy

3.5.1. Epidemiology

HCV affects an estimated 58 million people globally, with a prevalence of approximately 1–2% among pregnant women. The opioid epidemic has driven a resurgence of HCV transmission among women of reproductive age in high-income countries [56,57]. No effective vaccine or post-exposure prophylaxis exists for HCV. Direct-acting antivirals (DAAs) achieve sustained virological response (SVR) rates exceeding 95% in the general population [58].

3.5.2. Diagnosis

Universal antenatal screening for HCV is increasingly recommended. SMFM and ACOG now advocate universal opt-out HCV screening at the first prenatal visit [59,60]. The standard diagnostic algorithm begins with anti-HCV antibody detection; a reactive result should be followed by quantitative HCV RNA testing to confirm active viraemia, as approximately 20–30% of seropositive individuals have resolved infection [61].

3.5.3. Management

Major guidelines currently recommend deferral of HCV treatment to the postpartum period given limited prospective safety data on DAA exposure in early pregnancy [60]. However, this consensus is increasingly challenged by accumulating observational evidence and the ethical consideration of untreated curable infection during a period of healthcare

engagement [27]. Sofosbuvir-based regimens have not demonstrated apparent increase in adverse outcomes in emerging second and third trimester data, though prospective safety trials are awaited [27,58,62]. Prompt postpartum initiation of a pangenotypic DAA regimen should be offered to women not treated antenatally.

3.5.4. Pregnancy-Specific Considerations

The rate of vertical transmission of HCV is approximately 5–6%, rising to 10–15% in HIV co-infected women [63–65]. Current guidance recommends HCV RNA testing of exposed infants at approximately two months of age, with confirmatory antibody testing at eighteen months. HCV infection in pregnancy has been associated with intrahepatic cholestasis of pregnancy, gestational diabetes, preterm birth, and low birth weight [66]. Mode of delivery does not significantly influence HCV transmission rates and cesarean section is not routinely recommended on this basis.

3.6. Hepatitis D in Pregnancy

3.6.1. Epidemiology and Diagnosis

HDV is a defective RNA satellite virus entirely dependent on HBV for its replication, occurring exclusively in HBsAg-positive individuals [67]. Global HDV prevalence is estimated at approximately 5% among HBsAg-positive individuals, with high prevalence in Mongolia, sub-Saharan Africa, the Amazon Basin, and Eastern Europe [67,68]. All HBsAg-positive pregnant women should be screened with anti-HDV total antibody, followed by quantitative HDV RNA testing if reactive [68].

3.6.2. Management

There is no specific antiviral therapy currently approved for HDV in pregnancy. Bulevirtide, conditionally approved in Europe for non-pregnant adults, has not been evaluated in pregnancy. Pegylated interferon-alpha is absolutely contraindicated [46]. Management is focused on optimizing HBV suppression with TDF and multidisciplinary supportive hepatological care [68].

3.6.3. Pregnancy-Specific Considerations

HDV superinfection accelerates hepatic fibrosis and increases risks of cirrhosis and hepatocellular carcinoma, necessitating intensive monitoring throughout pregnancy [68]. Direct fetal data are lacking, but by analogy with other causes of severe maternal hepatic decompensation, HDV-associated flares are presumed to carry an increased risk of preterm birth and fetal growth restriction, underscoring the need for close antenatal surveillance in co-infected women. Crucially, comprehensive HBV immunoprophylaxis with HBIG and neonatal vaccination effectively prevents HDV perinatal transmission, as HDV cannot replicate without HBV [69]. Pregnancy-specific data for HDV are extremely limited, and recommendations are necessarily extrapolated from non-pregnant adult data and expert consensus.

3.7. Hepatitis E in Pregnancy

3.7.1. Epidemiology

HEV is estimated to affect approximately 20 million people annually worldwide, causing around 44,000 deaths. Crucially, pregnant women infected with genotype 1 HEV face a case fatality rate of 15–25%, vastly exceeding that in non-pregnant adults (0.5–3%). Genotypes 1 and 2 cause large waterborne epidemics in developing countries; genotypes 3 and 4 are zoonotic and cause sporadic infections in high-income countries [70,71].

3.7.2. Diagnosis

HEV should be considered in any pregnant woman with acute hepatitis, jaundice, or unexplained hepatic dysfunction, particularly in epidemic settings or after travel to endemic regions. Diagnosis is established by HEV-specific IgM antibodies; HEV RNA by RT-PCR is more sensitive, particularly in immunocompromised individuals [72]. Commercially available serological assays vary in sensitivity and specificity [23,73].

3.7.3. Management

There is no specific antiviral therapy approved for HEV in pregnancy. Ribavirin—effective in immunocompromised non-pregnant patients—is absolutely contraindicated due to potent teratogenicity. Management is entirely supportive, centered on nutritional support, fluid management, correction of coagulopathy, and vigilant monitoring for hepatic encephalopathy and acute liver failure [74]. A recombinant HEV vaccine (Hecolin) has demonstrated high efficacy in phase 3 trials but remains unlicensed outside China [75–77].

3.7.4. Pregnancy-Specific Considerations

The extraordinary maternal mortality associated with HEV genotype 1 reflects enhanced viral replication driven by sex hormones, altered T-cell responses, and heightened hepatic susceptibility [70]. Vertical transmission can occur with acute genotype 1 infection, with neonates potentially developing hypoglycemia, coagulopathy, and neonatal hepatitis [78]. There is no licensed vaccine or immunoglobulin for perinatal HEV prevention; management of exposed neonates is supportive. HEV in pregnancy represents a critical unmet need in global maternal health.

3.8. Comparative Analysis of Viral Hepatitis A–E in Pregnancy

A comparative analysis across all five hepatotropic viruses (Table 3) reveals clinically important distinctions. HEV carries the highest maternal mortality risk (case fatality rate 15–25% for genotype 1) [26,71]. HBV represents the most preventable perinatal infection: the combination of maternal TDF prophylaxis from 24–28 weeks and neonatal HBIG plus vaccine within twelve hours of birth reduces MTCT to below 1% [40,47]. HAV is preventable through vaccination, safe in pregnancy. HDV prevention is effectively achieved through comprehensive HBV immunoprophylaxis [69]. HCV and HEV currently lack licensed vaccines, leaving prevention dependent on harm reduction and public health measures.

Table 3. Comparative summary of viral hepatitis A–E in pregnancy.

Feature	HAV	HBV	HCV	HDV	HEV
Transmission	Fecal–oral	Perinatal, blood, sexual	Blood, perinatal	Perinatal (HBV-dependent)	Fecal–oral (waterborne)
MTCT Risk	Very rare	10–90% *	5–6% (up to 15% with HIV)	Prevented by HBV prophylaxis	Possible with genotype 1
Maternal Mortality	Rarely fatal	Low (without advanced disease)	Low	Elevated if superinfection/fulminant	15–25% (genotype 1)
Vaccine Available	Yes (safe in pregnancy)	Yes	No	Via HBV vaccine	Yes (Hecolin; China only)
Antiviral Therapy	Supportive only	TDF preferred	DAAAs (defer to postpartum)	TDF for HBV suppression	Supportive only (ribavirin contraindicated)
Neonatal Prophylaxis	Post-exposure Ig	HBIG + vaccine within 12 h	None available	Via HBV immunoprophylaxis	None available

* Range reflects HBeAg status and viral load—the lower bound (~10%) applies to HBeAg-negative mothers with low HBV DNA; the upper bound (>90%) applies to HBeAg-positive mothers with high viral load in the absence of prophylaxis.

HCV in pregnancy occupies the most contested therapeutic territory. The transformative efficacy of pangenotypic DAAs—achieving SVR exceeding 95%—has created both an opportunity and an ethical tension regarding treatment timing [27,58]. HDV is unique in being entirely biologically dependent on HBV; optimal HBV management simultaneously manages HDV, representing the only clinical example where prevention of one virus simultaneously eliminates another [67]. Table 3 provides a comparative summary of transmission route, mother-to-child transmission risk, maternal mortality, vaccine availability, antiviral therapy, and neonatal prophylaxis across all five hepatotropic viruses, and Figure 1 summarizes the overall diagnostic and management pathway across all three conditions reviewed in this article.

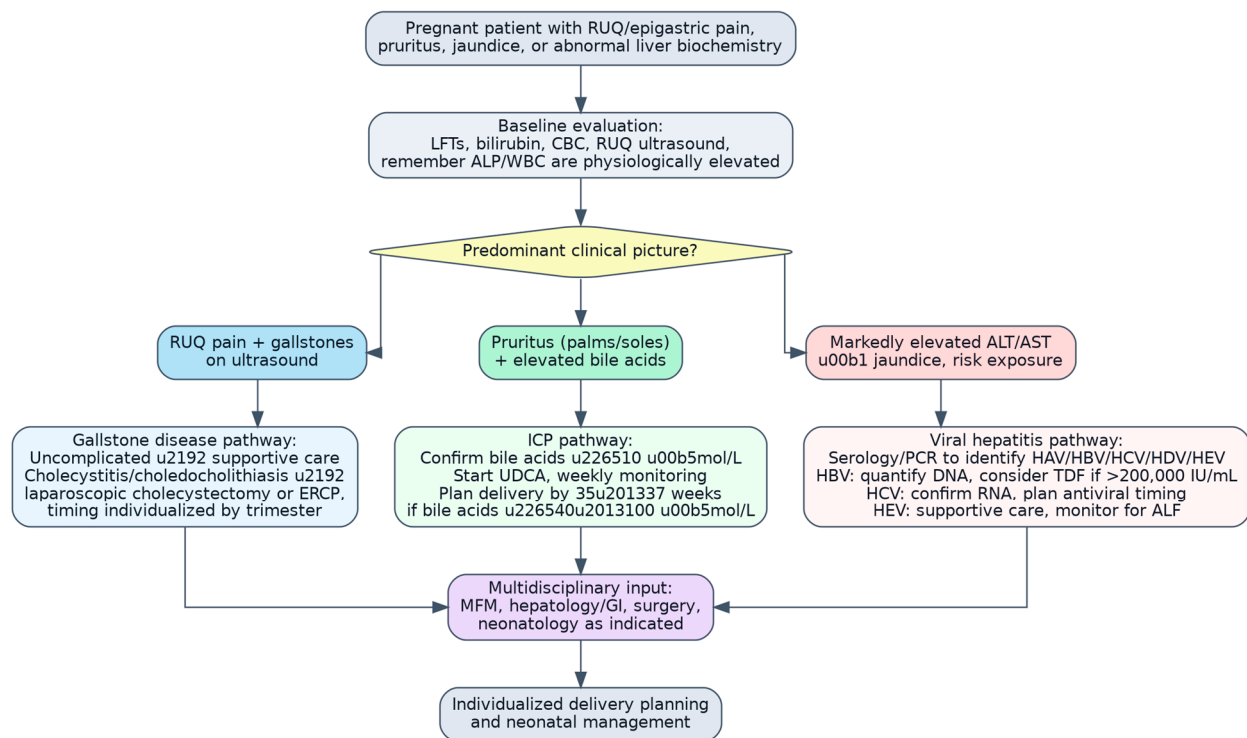


Figure 1. Simplified diagnostic and management algorithm for hepatobiliary disorders in pregnancy, spanning gallstone disease, intrahepatic cholestasis of pregnancy (ICP), and viral hepatitis. Trimester-specific and guideline-specific nuances discussed in the text should guide individualized management; this figure is intended as a bedside orientation tool rather than a substitute for the full text.

3.9. Discussion

Several overarching themes emerge from this synthesis (Figure 1). First, universal first-trimester screening for both HBV and HCV is the single highest-impact clinical action available. Risk-based approaches have consistently missed infected women and should be abandoned. The maternal TDF plus neonatal immunoprophylaxis strategy for HBV reduces MTCT to below 1%, yet the implementation gap in resource-limited settings remains the primary barrier to elimination [40,47,49].

Second, HCV management must evolve beyond blanket postpartum deferral; individualized antenatal treatment in the second trimester may be appropriate in carefully selected cases where barriers to postpartum re-engagement are high. A prospective first-trimester DAA safety trial is the primary outstanding evidence need [27,58,62]. Third, HEV in pregnancy is the most lethal and most neglected of the five viruses reviewed. Prioritizing global licensure of Hecolin for women of reproductive age in endemic settings is an urgent public

health imperative [75–77]. Fourth, the evidence base for HDV in pregnancy is critically thin and requires dedicated prospective cohort investment.

It is also important to distinguish, throughout this review, between recommendations that rest on high-level evidence (randomized trials, large registries, or meta-analyses) and those that reflect expert consensus extrapolated from limited or non-pregnant data. The HBV maternal-antiviral-plus-neonatal-immunoprophylaxis strategy and the diagnostic bile-acid thresholds for ICP are supported by randomized or large observational data. By contrast, several recommendations discussed above—including the specific timing of surgery for gallstone disease across trimesters, second-line agents for UDCA-refractory ICP, and essentially all HDV-specific guidance—are derived chiefly from cohort studies, retrospective series, or expert opinion, and are presented in guidelines with more confidence than the strength of the underlying literature strictly warrants. Readers should weigh the strength of the underlying evidence, not only the confidence with which a guideline states its recommendation.

A related source of complexity is that major professional societies do not always agree. For gallstone disease, SAGES and ACOG both now favor early surgery over conservative management, but neither issues a strict trimester-specific mandate, leaving timing to individualized clinical judgment. For ICP, RCOG recommends induction after 37 weeks whereas ACOG recommends delivery between 36 and 37 weeks, a discrepancy that can lead to inconsistent practice across institutions using different guideline references [19]. For HBV, AASLD, APASL, and EASL concur on a 200,000 IU/mL HBV DNA threshold for initiating antiviral prophylaxis and on tenofovir as the preferred agent, but differ in recommended initiation timing (24 vs. 28 weeks) and in the threshold at which lower-risk women are offered prophylaxis at all. Clinicians should therefore anchor their practice to whichever guideline is endorsed by their own institution or national body, using this review as a comparative summary rather than as a single authoritative protocol.

Beyond the virus-specific priorities above, several cross-cutting challenges warrant future research and implementation attention. Unresolved clinical questions include the optimal gestational-age threshold for surgical versus conservative management of complicated gallstone disease, the comparative efficacy of second-line agents (rifampin, cholestyramine, S-adenosyl-L-methionine) for UDCA-refractory ICP, and the safety of first-trimester direct-acting antiviral therapy for HCV. From an implementation standpoint, universal HBV and HCV screening, tenofovir prophylaxis, and timely neonatal immunoprophylaxis remain inconsistently available in low-resource settings where the burden of these diseases is highest; closing this gap depends as much on health-system financing and supply-chain access to point-of-care HBV DNA testing and tenofovir as on further clinical-trial evidence. Similarly, global licensure and distribution of the HEV vaccine outside China, and the development of pregnancy-specific dosing and safety data for second-line ICP agents, represent concrete, actionable research priorities rather than open-ended calls for “more study.”

4. Conclusions

Five key conclusions emerge from this synthesis. First, universal first-trimester screening for HBV and HCV must replace risk-based approaches. Second, HBV perinatal transmission is now preventable in virtually all settings; the outstanding challenge is implementation. Third, HCV management must evolve toward shared decision-making about antenatal DAA therapy in selected cases. Fourth, HEV is the most lethal and most neglected virus reviewed; global licensure of the HEV vaccine (Hecolin) is an urgent public health imperative. Fifth, the evidence base for HDV in pregnancy requires dedicated prospective cohort investment. A structured approach encompassing universal screening,

timely diagnosis, evidence-based antiviral therapy, coordinated neonatal prophylaxis, and multidisciplinary care is essential.

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