

Review Article: Fetal and Neonatal Health Consequences of Vertically Transmitted Hepatitis E Virus Infection

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Abstract. Hepatitis E virus (HEV) infections lead to tens of thousands of deaths annually, mostly in developing countries. Hepatitis E poses a significant threat to the health of expectant mothers, a well-noted epidemiologic feature of the disease, but the contribution of vertically transmitted HEV infection to fetal and neonatal morbidity and mortality has received limited attention. Evidence assembled to date suggests that mother-to-child HEV transmission may be frequent and deleterious to the fetus and newborn in pregnancies affected by hepatitis E. Additional work is required to resolve key questions. (1) What risks do subclinical maternal HEV infections and infections early in pregnancy pose to fetal health and development? (2) Does vertical transmission occur during labor and/or breastfeeding and contribute appreciably to neonatal morbidity and mortality? (3) How do treatment decisions for severely ill mothers affect fetal and neonatal outcomes? (4) Can maternal vaccination effectively prevent vertical transmission of HEV?

INTRODUCTION

Although hepatitis E virus (HEV) is sometimes referred to as an emerging infectious agent, it is well-established as a major cause of acute viral hepatitis (AVH) worldwide.¹ Of the more than 20 million infections estimated to occur globally each year ~70,000 infections result in death.² The vast majority of these deaths occurs in resource-poor countries in Asia, Africa, and Latin America, where exposure to fecally contaminated water results in outbreaks and sporadic cases of hepatitis E.^{2,3} Hepatitis E in these locations is nearly always attributable to the human-associated HEV genotypes 1 (Asia, Africa, and Latin America) and 2 (sub-Saharan Africa and Mexico). However, the globally ubiquitous zoonotic HEV strains (genotypes 3 and 4) have more recently been identified as a cause of sporadic hepatitis in medically vulnerable patients and the general population in high-income countries.^{4–14}

High case-fatality ratios among pregnant women, particularly during the third trimester of pregnancy, remain an almost pathognomonic feature of hepatitis E epidemics caused by HEV genotype 1.^{15–21} There is mounting evidence that hepatitis E is an important contributor to maternal morbidity and mortality in south Asia, even outside of periodic large outbreaks.^{22–26} In the early literature on hepatitis E, there was much conjecture about the extent to which maternal hepatitis E threatened fetal and neonatal health beyond catastrophic maternal illness or death. Emerging evidence from epidemiologic and clinical studies now suggests that vertical transmission of HEV may occur frequently among mothers ill with hepatitis E and contribute to serious perinatal health outcomes along with the effects of maternal morbidity and mortality.

HEPATITIS E AND MATERNAL–CHILD HEALTH

Epidemic jaundice marked by an excess of illness and death among pregnant women and their infants has been documented at least as far back as 18th century Europe.^{15,27} The first (retrospectively) serologically confirmed hepatitis E outbreak occurred in Delhi, India in the mid-1950s,^{17,28,29} although molecular evidence suggests that HEV may already

have been circulating in humans for several hundred years.^{30,31} A hospital-based study during the Delhi epidemic documented an ~10% maternal case-fatality rate along with miscarriage, stillbirth, or neonatal death in 56% of infants of women with HEV infection. In addition, jaundice was reported among both expiring and surviving infants.¹⁶

Numerous studies conducted over the three decades since HEV was identified as a cause of infectious hepatitis³² have continued to support high rates of maternal, fetal, and neonatal illness and death in affected pregnancies. According to one recent model, HEV may be responsible for ~2,400–3,000 stillbirths each year in developing countries,^{2,33} with many additional fetal deaths linked to antenatal maternal mortality.³⁴ Preterm delivery in mothers with hepatitis E is common and associated with poorer neonatal survival.^{33,35} During a 2002 outbreak in the Central African Republic, all of the pregnant women with serologically confirmed hepatitis E ($N = 7$) delivered prematurely; three of these babies were stillborn (one macerated), and another baby died within minutes of delivery.³⁶ Newborns whose mothers had acute hepatitis at the time of delivery comprised one-half (4/8) of the fatalities in a 1993–1994 outbreak in Islamabad, Pakistan.²¹ Pregnant women with jaundice during a 2008–2009 hepatitis E outbreak in Tongi, Bangladesh were more than two times as likely as non-jaundiced pregnant women to miscarry or deliver a stillborn baby.³⁷ In two separate hospital-based prospective studies in New Delhi and Chennai, India, ~15% to > 50% of the live-born infants of mothers with hepatitis E died within the first 1 week post-partum.^{33,38} During a 2010–2011 outbreak in Sudan, 14 intrauterine deaths and 9 premature deliveries were reported among 39 pregnant hepatitis E cases.³⁹

To date, only hepatitis E caused by HEV genotype 1 has consistently been observed to yield these effects in pregnancy. However, HEV genotype 2 was implicated in acute liver failure in a pregnant woman during an outbreak in Namibia,⁴⁰ and the potential of genotypes 2–4 to cause adverse outcomes in pregnant women, given exposure, remains uncertain.

MISCARRIAGE AND STILLBIRTH: THE ROLE OF ANTENATAL HEV INFECTION

Despite the ample epidemiologic evidence that maternal hepatitis E may result in adverse consequences to the fetus,

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few studies have been able to address whether these outcomes are solely the result of maternal health complications, or whether fetal HEV infection also plays a role. Etiologic studies of pregnancy loss and stillbirth are complicated by numerous logistical, technical, cultural, and ethical obstacles.⁴¹⁻⁴⁴ The prospective design, sample size, and frequency of perinatal observations and follow-up would require considerable resources and advanced clinical and research infrastructure. As a result, the task of showing a contribution of fetal HEV infection to intrauterine or intrapartum death has rarely been attempted.

Early research in China failed to detect HEV antigen (HEVAg) in any of 17 stillborn fetuses with mothers who were infected during a 1986-1988 outbreak.⁴⁵ In a case-control study in Egypt, HEVAg was detected in 5% of aborted fetal tissue samples but absent from the cord blood of live-born, full-term infants.⁴⁶ Anti-HEV immunoglobulin M (IgM) was detected in 3% and HEV RNA was detected in 16% of mothers who aborted, but they were not detected in mothers who delivered live infants.⁴⁶ Although these Egyptian results support an association of HEV with abortion, they fall short of implicating antenatal HEV transmission to the fetus as a cause of fetal death.

Results in other animals have been similarly inconclusive. Experimental inoculation studies of HEV genotype 1 in pregnant rhesus macaques^{47,48} and genotype 3 in swine⁴⁹ have failed to provide clear evidence of vertical transmission or adverse pregnancy outcomes attributable to HEV. Of four pregnant macaques inoculated with an epidemic HEV strain isolated from an Indian patient in 1990, three delivered healthy infants (two of them after elevation of liver enzymes), whereas the remaining macaque delivered a macerated fetus 5 days before the onset of hepatitis.⁴⁸ Consistent with other experimental studies of HEV involving animal models,⁵⁰ the disease provoked in these pregnant animals was less severe than the disease seen in most pregnant women who come to clinical attention.

Investigation of adverse gestational outcomes among naturally infected animals has also yielded results that are challenging to interpret. HEV genotype 3 RNA was amplified from the livers of ~16% of aborted porcine fetuses on two South Korean farms.⁵¹ Concomitant detection of porcine circovirus-2 (PCV2) in all of these fetal pig samples casts doubt on the role of HEV in these deaths, but it also raises the important question of whether coinfection with immunosuppressive viruses may facilitate fetal infection with HEV.⁵¹

In south and central Asia and sub-Saharan Africa, where genotypes 1 and 2 predominate, no human studies have systematically evaluated the association of fetal HEV infection with miscarriage or stillbirth. Therefore, it remains unclear whether some of the increased risk of miscarriage and stillbirth reported in these diverse settings may be attributable to vertically transmitted infection or whether it is the result of maternal complications of hepatitis E alone.

HEV INFECTION AND OUTCOMES AMONG LIVE-BORN INFANTS

Morbidity and mortality among neonates born to mothers with hepatitis E may be explained, to a large extent, by pre-term delivery and other pre- and perinatal stresses caused by the maternal response to infection. However, a small body of evidence suggests that vertically transmitted infections also contribute directly to infant morbidity and mortality in the early post-natal period.

A landmark study published in 1995 by Khuroo and others⁵² was the first to document mother-to-child transmission of HEV using serologic and molecular methods. HEV RNA was found in the cord blood of five of eight Kashmiri infants whose mothers had serologic evidence of infection preceding delivery.⁵² All five of these infants had elevated alanine aminotransferase (ALT) at birth. Two infants died within 1 day of delivery.⁵² Serum viremia, IgM antibodies, and hepatitis persisting for several weeks in two of the surviving infants suggested that these results could not be explained solely by contamination of cord blood with maternal blood and that vertically transmitted HEV could, in fact, cause illness in neonates.⁵²

Subsequent studies have found a similarly high prevalence of vertically transmitted HEV infection (Table 1),⁵³⁻⁵⁷ which frequently, but not always, results in disease. Hepatitis, either icteric or anicteric, may be present from birth in a substantial proportion of neonates born to mothers with hepatitis E.^{58,59} Recently, a second trimester fetal HEV infection associated with ascites was reported to have resolved *in utero*, resulting in a healthy infant who was born at 38 weeks of gestation.⁶⁰ However, evidence of severe necrosis in liver tissue samples from neonatal autopsies suggests that some babies, like their mothers, experience fulminant hepatic failure (FHF) as a result of HEV infection.⁵³

TABLE 1

Vertically transmitted HEV infection, morbidity, and mortality in live-born infants of mothers with laboratory-confirmed antenatal HEV infection

Study characteristics	Live births tested	HEV infections in neonates (% of live births)	Hepatitis E cases in neonates (% of live births)	Icteric hepatitis E cases in neonates (% of live births)	Neonatal deaths (% of live births)
Srinagar, India ⁵³ : 20 mothers with AVH, 16 mothers with FHF	33	22 (67); ≥ 17 RNA+; ≥ 21 IgM+	22 (67)	20 (61)	11 (33)
New Delhi, India ^{54,55} : 19 mothers with AVH, 9 mothers with FHF	18	6 (33); 4 RNA+; 3 IgM+	No data	No data	No data
New Delhi, India ⁵⁶ : 8 mothers with AVH, 14 mothers with FHF	6	3 (50); 3 RNA+	1 (17)	1 (17)	0 (0)
Accra, Ghana ⁵⁷ : 1 mother with AVH, 2 mothers with FHF	1	1 (100)	1 (100)	1 (100)	0 (0)

Among mothers, serological testing was performed for hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections in the Srinagar- and New Delhi-based studies. No coinfections were reported by Khuroo and others⁵² in Srinagar. Two HBV + HEV coinfections and 1 HCV + HEV coinfection were reported by Kumar and others⁵⁴ and Singh and others⁵⁶ in each of the two New Delhi-based studies. The mother of the tested neonate in the Ghana study by Bonney and others⁵⁷ was initially suspected of having malaria and viral hepatitis coinfection, but confirmation of a malaria diagnosis was not reported. Aside from the Ghana study, none of the studies provided sufficient detail to assign specific outcomes to the infants of mothers with coinfections. Laboratory-confirmed antenatal HEV infection means detection in maternal serum of anti-HEV IgM, HEV RNA, or both at any time during the pregnancy or at delivery; most cases occurred in the third trimester.

In contrast to perinatally transmitted hepatitis B virus infections, which may be lifelong if preventive measures are not initiated at birth,⁶¹ there have been no reports of persistent HEV infection in infants born to mothers with hepatitis E.⁶² This finding is consistent with the natural history of hepatitis E in adults, which is typically self-limiting.⁶³ Chronic HEV infections have been reported primarily in immunosuppressed and immunocompromised populations.^{9,63–82} They have not been documented in pregnant women or infants, although some authors have speculated that, among immunocompromised pregnant women or neonates, such infections could, plausibly, be of concern.⁸³ In addition, pregnant women may be coinfecting with other hepatotropic pathogens,^{54,56,84–89} but how such coinfections influence vertical HEV transmission and outcomes has not been studied.

CHALLENGES IN UNDERSTANDING MOTHER-TO-CHILD TRANSMISSION OF HEV

Limited surveillance and reporting have presented obstacles to understanding the consequences of HEV infections on maternal, fetal, and neonatal outcomes. Misclassification of HEV infection because of barriers to medical care,^{90,91} failure to consider hepatitis E in differential diagnosis,^{92–95} or use of insensitive assays⁹⁶ may obscure the impact of HEV on pregnancy outcomes.

In addition, study populations in the reported literature are largely hospital-based and skewed to women with more severe illness and, thus, a predisposition to having worse fetal and/or neonatal outcomes. Nonetheless, results from the largest prospective studies of women with hepatitis E paint a picture of relatively poor pregnancy outcomes, even in women with milder illness and not only among those women with acute liver failure.^{33,97}

The extent to which asymptomatic infections influence pregnancy outcomes has not yet been studied systematically. In addition, there are no reliable data on whether HEV can be transmitted through breast milk. Population-based serologic surveillance of pregnant women and follow-up of pregnancy and neonatal outcomes may help to address these issues. Furthermore, studies are needed across a wider variety of settings. Differences in viral characteristics,⁹⁸ exposure patterns,⁹⁹ underlying population health and nutrition status,¹⁰⁰ host genetics,¹⁰¹ and other host factors may modify the effects of maternal HEV infection on fetal and neonatal outcomes.

Additional investigation of the mechanisms of HEV pathogenesis in pregnant women would help in understanding the role of transplacental transmission in fetal loss and stillbirth. The timing of HEV infection relative to pregnancy may also be a critical variable. Although the preponderance of severe hepatitis E in pregnant women occurs during the third trimester, how this observed maternal response relates to vertical transmission and fetal viability has not yet been elucidated.

It has been suggested that *in utero* fetal infection may itself contribute to adverse maternal outcomes.⁵³ Such upside-down vertical effects have been posited to occur with other viral infections as well. Studies of murine γ -herpesvirus 68 in mice, for example, have found that fetal inflammatory responses to viral replication in the placenta may pre-dispose the mother to morbidity and reduce the mother's capacity for sustaining the pregnancy.^{102,103} Hormone receptor-modulated inflammatory

responses at the fetomaternal interface have been associated with pregnancy outcomes in human hepatitis E.⁹⁷

There are currently no adequate treatments for hepatitis E in pregnancy. Experimental use of ribavirin has recently shown promise in treating severe acute hepatitis E in non-pregnant patients,^{104–106} but this drug is typically contraindicated in pregnancy because of “significant embryocidal and/or teratogenic effects” and fetal harm.¹⁰⁷ Some researchers have suggested that expedited delivery or pregnancy termination could be considered to preserve the life of the mother.^{53,108} Whether this approach would prevent death in women who present with severe disease has not been studied systematically. Given the high rates of miscarriage, stillbirth, and premature delivery in pregnancies affected by severe hepatitis E, the net impact of such a strategy on neonatal morbidity and mortality is also uncertain.

New HEV vaccines show promise in preventing hepatitis E,^{109,110} and they may help obviate the need for treatment of severe illness. However, follow-up data indicate that HEV infections can still occur among vaccinated adults,¹¹¹ and only incidental data on safety and efficacy in pregnant women are available.¹¹² Evaluating the effectiveness of these vaccines in preventing maternal disease and death and reducing the burden of fetal loss, premature delivery, and neonatal morbidity and mortality should stand among global maternal-child health priorities.

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