






ORIGINAL ARTICLE

Maternal and fetal outcomes of pregnancies complicated by acute hepatitis E and the impact of HIV status: A cross-sectional study in Namibia

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Abstract

Background & Aims: Namibia has been suffering from an outbreak of hepatitis E genotype 2 since 2017. As nearly half of hepatitis E-related deaths were among pregnant and postpartum women, we analysed maternal and fetal outcomes of pregnancies complicated by acute hepatitis E and assessed whether HIV-status impacted on outcome.

Methods: A retrospective cross-sectional study was performed at Windhoek Hospital Complex. Pregnant and postpartum women, admitted between 13 October 2017 and 31 May 2019 with reactive IgM for Hepatitis E, were included. Outcomes were acute liver failure (ALF), maternal death, miscarriage, intra-uterine fetal death and neonatal death. Odds ratios (OR) and 95% confidence interval (CI) were calculated.

Results: Seventy women were included. ALF occurred in 28 (40.0%) of whom 13 died amounting to a case fatality rate of 18.6%. Sixteen women (22.9%) were HIV infected, compared to 16.8% among the general pregnant population (OR 1.47, 95% CI 0.84-2.57, $P = .17$). ALF occurred in 4/5 (80%) HIV infected women not adherent to antiretroviral therapy compared to 1/8 (12.5%) women adherent to antiretroviral therapy (OR 28.0, 95% CI 1.4-580.6). There were 10 miscarriages (14.3%), five intra-uterine fetal deaths (7.1%) and four neonatal deaths (5.7%).

Conclusions: One in five pregnant women with Hepatitis E genotype 2 died, which is comparable to genotype 1 outbreaks. Despite small numbers, HIV infected women receiving antiretroviral therapy appear to be less likely to develop ALF in contrast with HIV infected women not on treatment. As there is currently no curative treatment, this phenomenon needs to be assessed in larger cohorts.

KEYWORDS

hepatitis E virus, HIV, maternal mortality, Namibia

Abbreviations: ALF, Acute liver failure; ART, Antiretroviral therapy; CFR, Case fatality rate; CI, Confidence interval; HEV, Hepatitis E virus; ICU, Intensive care unit; IgM, Immunoglobulin M; INR, International normalized ratio; OR, Odds ratio.

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1 | INTRODUCTION

Hepatitis E virus (HEV) is a leading cause of acute viral hepatitis in low- and middle-income countries, with an estimated 20.1 million HEV infections and 70 000 deaths annually.¹ Epidemiology and clinical presentation differ in the four main genotypes that may infect humans. Genotypes 1 and 2 are transmitted via contaminated drinking water, and outbreaks are mainly seen in Asia and Africa in regions with poor sanitation, whereas genotypes 3 and 4 are transmitted through infected swine meat and more common in high-income countries and Asia.²⁻⁴ Usually, HEV infection is self-limiting with a low mortality rate. However, during pregnancy, a severe clinical course is frequently seen with fulminant hepatic failure, high case fatality rates and high rates of fetal complications such as miscarriage, stillbirth or premature birth. These considerable adverse outcomes are particularly described in areas where genotype 1 is endemic, and confirmed in reports from genotype 2 endemic areas, which is far less prevalent. However, it has not been identified in genotype 3 and 4 endemic areas.^{5,6} The pathogenesis of the severe clinical course in pregnant women is not fully understood. It has been suggested that it may be related to the suppressed cellular immunity and immune response in general in pregnancy.⁶ Currently there is no approved effective treatment available for acute HEV infections.^{7,8}

Namibia has been suffering from an outbreak of HEV genotype 2 since December 2017, with more than 6000 infections reported from all 14 regions by August 2019.⁹ Nearly half of the deaths because of HEV were among pregnant and postpartum women and HEV became the leading cause of maternal deaths in 2018-2019.^{9,10} Namibia had a high HIV prevalence estimated at 12.6% among adults aged 15-64 years in 2017.¹¹ The impact of HIV/HEV co-infection on outcome is not yet clear. Some studies reported a higher seroprevalence of HEV among people with HIV in the general population, while others could not confirm this finding.^{12,13} Infection with HEV genotype 3 can develop into a chronic infection among immunosuppressed patients, including HIV-infected persons with a low CD4 count, but this has not been described for the other genotypes.^{4,12} Considering pregnant women there is hardly any data on HIV/HEV co-infection since most previous genotype 1 and 2 outbreaks occurred in regions with a low HIV prevalence.

As data on outcome of hepatitis E in pregnant women in the setting of an HEV genotype 2 outbreak are still scarce, in particular with a focus on HIV infected women, our aim was to analyse maternal and fetal outcomes of pregnancies complicated by acute HEV in Namibia and assess whether HIV status had clinical implications in our cohort.

2 | METHODS

2.1 | Study design and setting

This retrospective cross-sectional study was performed in Windhoek Hospital Complex, which has around 12 000 births annually. The first HEV case of the outbreak in Namibia was

Lay summary

We assessed the outcomes of pregnancy in women infected with hepatitis E in Namibia. One in five women who had acute hepatitis E during their pregnancy died, one in seven had a miscarriage and one out of eight babies died before or after birth. Women who were also infected with HIV, appear to be less frequently critically ill, especially when they were on treatment for HIV.

Key points

- We analysed maternal and fetal outcomes of pregnancies complicated by acute hepatitis E during an outbreak in Namibia caused by genotype 2.
- One in five pregnant women with acute hepatitis E died.
- One in four pregnancies of women with acute hepatitis E resulted in a miscarriage, intra-uterine fetal death or neonatal death.
- Women in the third trimester were at higher risk for acute liver failure.
- Despite small numbers, HIV infected women receiving antiretroviral therapy appear to be at lower risk to develop acute liver failure, in contrast to HIV infected women not on treatment.

reported on 13 October 2017 in Khomas region, in which the capital Windhoek is located. The outbreak continued in the city and by August 2019, there were 6151 reported cases nationally and the outbreak had spread to 10 of the 14 regions with sporadic cases in the other regions as well.⁹ The national case fatality rate (CFR) was 0.9% with 56 fatalities.⁹ The majority of HEV cases were reported to be among people from informal settlements. These settlements are densely populated with limited access to sanitation, safe drinking water and hygiene. Most people live in the capital for work but travel to different parts of the country to visit family members several times a year. This continuous movement to different regions has likely facilitated the spread of HEV throughout the country. In 2018, two blood samples were tested for genotyping and showed HEV genotype 2. There are reports from two previous outbreaks in Namibia. Both were in the informal settlements of Rundu, a town in northern Namibia, of which the first outbreak was in 1983 because of HEV genotype 1 and the second outbreak in 1995 because of genotype 2.^{14,15} Whereas most outbreaks last on average a year, the outbreak in Namibia which started in 2017 has been ongoing for more than 3 years.²

According to the national HIV guidelines, all adults with HIV are started on antiretroviral therapy (ART) in Namibia, regardless of CD4 count or clinical stage.¹⁶ In comparison to their neighbouring

countries, Namibia performs well in implementation of the ART services: in 2017, 97.1% of HIV-infected females were on ART and of these, 92.2% were virally suppressed.¹¹

2.2 | Study population and data collection

All pregnant women and women whose birth was terminated less than 42 days earlier, who were admitted to Windhoek Hospital Complex between 13 October 2017 and 31 May 2019 with acute HEV, confirmed by a reactive HEV immunoglobulin M (IgM), were eligible for inclusion in this study. Women were excluded if no positive IgM test result was available, the woman was not admitted to a health facility, her pregnancy or recent pregnancy could not be confirmed, or her clinical file could not be traced. The Ministry of Health and Social Services, together with the World Health Organization, developed clinical management guidelines, recommending all pregnant and postpartum women with jaundice to be admitted and tested for reactive HEV IgM, regardless if other clinical symptoms were present. Therefore, many women with mild disease were admitted and included in our cohort.

Cases were identified using a list of all suspected HEV cases in Khomas region from the Ministry of Health and Social Sciences of Namibia, which was established from the start of the outbreak, as hepatitis E is a notifiable disease. Because of budget restrictions, it was not possible to apply this list to other affected regions. Nevertheless, our cohort included the majority of pregnant women with HEV in Namibia, as the capital and its referring regions were most severely affected by the outbreak. In the referring regions intensive care unit (ICU) facilities were not available and nearly all pregnant women with a confirmed HEV infection were therefore transferred to our study site for further monitoring and care. In the hospital complex the capital ICU facilities were available to provide supportive care for patients with ALF.

For identification of possible missed cases, data from the National Maternal Death Review Committee of the Ministry of Health and Social Services was used. This committee analysed all maternal deaths occurring in the country between 1st of April 2018 and 31st of March 2019 and all cases of severe morbidity between 1st of March 2018 and 31st of May 2018 in the capital and between 1st of October 2018 till 31st of March 2019 nationally.^{10,17,18} Considering the severe clinical course among pregnant women, these cohorts contained many women with complicated pregnancies because of HEV.

For identified cases, data were collected anonymously from medical records using a structured data collection tool, including socio-demographic characteristics, maternal outcomes, fetal outcomes, obstetric complications, signs of liver failure and HIV status. This was done by AH and MC and verified by SH and MJ, both medical doctors with several years of experience providing obstetric care in Namibia.

Laboratory test results on admission and the most abnormal value during admission were collected from the database of the National Institute of Pathology, including alanine aspartate aminotransferases, alanine aminotransferases, bilirubin, haemoglobin, platelets, creatinine and international normalized ratio (INR).

Serology test for hepatitis A, B and C were performed by Alinity Abbott. Hepatitis E serology was performed using Aria rapid tests. Glucose values were obtained through capillary blood tests. If the woman was HIV infected, data on ART treatment adherence, latest CD4 count and viral load value were retrieved from medical records, the database of the National Institute of Pathology and additional information was collected through the ART clinic the patient was attending. Data regarding fetal outcome was obtained from the woman's medical record. If a neonate had been admitted to neonatal ICU, survival status was obtained from neonatal ICU admission records. No neonate was tested for vertical transmission of HEV, as PCR testing was not available. HIV prevalence among the general pregnant population was collected through the Prevention Mother to Child Transmission Program of the Ministry of Health and Social Services.

2.3 | Outcomes and data analysis

Main maternal outcomes were number of women with acute liver failure (ALF) and death. ALF was defined according to the definition of European Association for the Study of the Liver; acute abnormality of liver blood tests (elevated serum transaminases) in an individual without underlying chronic liver disease followed by hepatic encephalopathy of any grade and a INR > 1.5.¹⁹ Severity of hepatic encephalopathy was graded using the West Haven Criteria, ranging from grade 1 with mild altered mental stage up to grade 4 which is complete coma. Acute hepatitis B was identified with a reactive test for IgM anti-HBc. Chronic hepatitis B was diagnosed when a woman had a reactive test for both HBsAG and anti-HBc. Hypoglycaemia was defined as any capillary blood glucose <4.0 mmol/L. Postpartum haemorrhage was defined as >1000 mL blood loss after birth. Premature birth was defined as birth between 26 weeks and 0 days of gestation and 36 weeks and 6 days. Intra-uterine fetal death was defined as a death before birth in a fetus with a gestational age of 26 weeks and 0 days or more. For miscarriage, the threshold of less than 26 weeks and 0 days was used. Neonatal death was death during the first 28 days of life. All results were reported as numbers (n) and frequencies (%). An ART defaulter was defined as any woman who interrupted her treatment and missed at least one clinic visit.¹⁶ Maternal case fatality rate was defined as the number of maternal deaths divided by the number of pregnancies complicated by acute hepatitis E and presented as a percentage. Fetal case fatality rate was defined as the number of intra-uterine fetal deaths and neonatal deaths, divided by the number of pregnancies complicated by acute hepatitis E and presented as a percentage.

Continuous variables are presented as means with standard deviations and differences in normally distributed variables were assessed using a student *t*-test. Missing data were assumed to be 'no' for categorical data, whereas complete case analysis was used to handle missing data for continuous variables and data regarding ART adherence. Categorical variables are presented as percentages. Differences were assessed using chi-square test or Fisher's Exact test when indicated and odds ratios (OR) with 95%

confidence intervals (CI) are presented. Statistical significance was assumed at a two-sided value of $P < .05$. Data analysis was performed with SPSS version 26. We followed the STROBE reporting guidelines.

3 | RESULTS

Seventy women were included into this study. The Ministry data identified 196 women who had been pregnant or recently pregnant and suspected to have contracted hepatitis E. Of these, 57 women had not been admitted to a health facility or tested for HEV. Four women had a negative IgM result and for 59 women it was indicated they were tested for HEV, but no IgM result could be found on the system. We were unable to trace medical records of 20/76 women, so 56 women were included in our study from the Ministry's data. An additional 14 women were identified through the national severe morbidity and mortality registries. Table 1 shows the baseline characteristics of the 70 women in our cohort.

3.1 | Maternal outcome

ALF occurred in 28/70 (40.0%) women, of whom 13 died leading to a maternal case fatality rate of 18.6%. Twelve women died because of fulminant liver failure after being in ICU for several days with hepatic encephalopathy grade 4 and one woman died because of hypovolemic shock secondary to postpartum haemorrhage and disseminated coagulopathy. Table 2 compares the characteristics of women who developed ALF and women without ALF. Women with ALF, compared to women without ALF, were more frequently in the third trimester, OR 3.45 (95% CI 1.10-10.83, $P = .04$), had one or more episodes of hypoglycaemia, OR 4.41 (95% CI 1.54-12.66, $P = .01$), and had a higher INR (6.2 ± 3.1 , compared to 1.7 ± 0.7 , $P < .01$). Women with ALF were more likely to give birth or lose their pregnancy because of a miscarriage compared to women without ALF during their admission for acute HEV, OR 4.63 (95% CI 1.20-17.93, $P = .03$). Of the women with ALF, 20/28 (71.4%) developed hepatic encephalopathy grade 4 and 24/28 (85.7%) needed mechanical ventilation. An INR >1.5 was found in 42/70 (60.0%) of our study population. We identified a trend of higher elevated serum transaminases for women with ALF. For six patients with ALF birth was complicated by postpartum haemorrhage. Two women developed pregnancy-induced hypertension and four had pre-existent hypertension. There were no other hypertension-related complications such as pre-eclampsia/eclampsia.

3.2 | HIV

In our study population 16/70 (22.9%) women were HIV infected, compared to a prevalence of 16.8% among the general pregnant population in Namibia in 2018, which was not significantly higher

TABLE 1 Baseline characteristics

	N = 70 (%)
Age (y)	
<20	3 (4.3)
20-34	60 (85.7)
≥ 35	7 (10.0)
Parity	
Para 0	9 (12.9)
Para 1-3	51 (72.9)
≥ 4	8 (11.4)
Unknown	2 (2.9)
Gestational age on admission (weeks + days)	
<13 + 0	6 (8.6)
13 + 0-25 + 6	14 (20.0)
26 + 0-36 + 6	34 (48.6)
$\geq 37 + 0$	5 (7.1)
Unknown	11 (15.7)
HIV status	
Positive	16 (22.9)
Negative	52 (74.3)
Unknown	2 (2.9)
Hepatitis	
Hepatitis A	0 (0)
Hepatitis B, acute	0 (0)
Hepatitis B, chronic	4 (5.7)
Hepatitis C	0 (0)
Pregnancy outcome	
Vaginal birth	37 (52.9)
Caesaren section	5 (7.1)
Miscarriage	10 (14.3)
Still pregnant at discharge	18 (25.7)
Maternal outcome	
Died	13 (18.6)
Survived	53 (75.7)

Note: Values are n (%).

(OR 1.47, 95% CI 0.84-2.57, $P = .17$).¹⁰ Among the women with ALF, HIV prevalence was lower compared to women without ALF (17.9% vs 26.2%), but there was no statistical significance (OR 0.61, CI 0.19-2.01, $P = .56$). Notably 4/5 HIV infected women who interrupted their ART (80%) developed ALF compared to 1/8 (12.5%) HIV infected women adherent to their ART (OR 28.0, 95% CI 1.4-580.6, $P = .03$). Table 3 presents the ART regimen, adherence, most recent available CD4 count and viral load of all HIV-infected women in our study. One woman with ALF forgot her ART when she was admitted for observation with HEV infection during pregnancy in a stable condition. She developed encephalopathy 5 days after admission and was transferred to ICU where she developed hepatic encephalopathy grade 3. Her ART was restarted 7 days after admission and she fully recovered. For three women we were unable to trace

TABLE 2 Characteristics of women with acute liver failure compared to no acute liver failure

Total	ALF	No ALF	All women	OR (95% CI)	P value
	n = 28	n = 42	n = 70		
Age	26.5 ± 4.8	28.7 ± 5.7	27.8 ± 5.4		.11
Third trimester ^a	23 (82.1)	24 (57.1)	47 (67.1)	OR 3.45 (1.1-10.8)	.04
Pregnancy outcome at discharge					
Given birth/miscarried	25 (89.3)	27 (64.3)	52 (74.3)	OR 4.63 (1.2-17.9)	.03
Still pregnant	3 (10.7)	15 (35.7)	18 (25.7)		
HIV-status	5 (17.9)	11 (26.2)	16 (22.9)	OR 0.61 (0.2-2.0)	.56
On ART	1 (20.0)	7 (63.6)	8 (50.0)	OR 0.14 (0.0-1.8)	.28
ART defaulted/interrupted	4 (80.0)	1 (9.1)	5 (31.3)	OR 28.0 (1.4-580.6)	.03
Unknown if on treatment	0 (0)	3 (27.3)	3 (18.8)		
Encephalopathy	28 (100)	0 (0)	28 (40.0)		
None	0 (0)	0 (0)	42 (60.0)		
Grade 1	1 (3.6)	0 (0)	1 (1.4)		
Grade 2	0 (0)	0 (0)	0 (0)		
Grade 3	6 (21.4)	0 (0)	6 (8.6)		
Grade 4	20 (71.4)	0 (0)	20 (28.6)		
Grade not specified	1 (3.6)	0 (0)	1 (1.4)		
Hypoglycemia	21 (75.0)	17 (40.5)	38 (54.3)	OR 4.41 (1.5-12.7)	.01
Mechanical ventilation	24 (85.7)	0 (0)	24 (34.3)		
INR	6.2 ± 3.1	1.7 ± 0.7	3.4 ± 2.9		<.01
AST IU/L admission	2874 ± 2232	1925 ± 1610	2302 ± 1924		.06
AST IU/L highest	3118 ± 2579	2487 ± 1725	2734 ± 2106		.27
ALT IU/L admission	1827 ± 847	1512 ± 1150	1634 ± 1047		.23
ALT IU/L highest	1929 ± 983	1770 ± 1111	1832 ± 1058		.55
Total bilirubin mg/dL admission	225 ± 95	183 ± 101	199 ± 100		.10
Total bilirubin mg/dL highest	278 ± 109	223 ± 132	244 ± 126		.08

Note: Values are mean ± standard deviation, n (%) and odds ratio (95% confidence interval).

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferases; ARV, anti retroviral treatment; AST, alanine aspartate aminotransferases; CI, confidence interval; INR, international normalized ratio; OR, odds ratio.

^a≥26 weeks completed weeks of gestation.

information regarding their ART regimen or adherence, of whom one woman had a recent viral load blood test indicating she was virally suppressed and therefore on treatment.

Twelve (75.0%) HIV positive women were in the third trimester, compared to 35/54 (64.8%) HIV negative women, which was not a significant difference ($P = .45$). For women in the third trimester, there was a trend of a lower HIV prevalence in women with ALF compared to women without ALF (17.4% vs 33.3%, OR 0.42, 95% CI 0.11-1.66, $P = .21$).

3.3 | Fetal outcome

Even though only 5/70 (7.1%) of the women had a term pregnancy at the time they were admitted with acute HEV, 42/70 (60.0%) gave birth during admission for HEV and 10/70 (14.3%) had a miscarriage. One woman died while still pregnant and only 17/70 (24.3%) were discharged

still pregnant after they had recovered from their HEV infection. There were five intra-uterine fetal deaths and four neonatal deaths leading to a fetal-neonatal case fatality rate of 12.9%. Six neonates were admitted to neonatal ICU and we were unable to verify whether they were discharged alive. One woman gave birth at 35 weeks of gestation but was admitted postpartum with signs of ALF and no information regarding fetal outcome was available. Figure 1 presents the fetal outcome of our cohort, according to gestational age at the time of HEV infection. Preterm birth took place among 30/70 (42.9%) women and 20 neonates needed admission to neonatal ICU for this reason.

4 | DISCUSSION

In our cohort of pregnant women with acute hepatitis E in the setting of an HEV genotype 2 outbreak we identified a high maternal case

TABLE 3 Details of HIV positive women with acute hepatitis E during pregnancy

	Outcome	Gestational age	ARV adherence	ARV regimen	CD4 cells/mm ³	Viral load (copies/mL)	Comments
1	ALF—died	3rd trimester	On treatment	TDF/3TC/ AZT/ATVr		<20 copies	2nd line regimen ^a
2	ALF—died	3rd trimester	Defaulted	N/A	279		
3	ALF—survived	3rd trimester	Defaulted		739		
4	ALF—survived	3rd trimester	Defaulted	TDF/3TC/EFV	560		Restarted in ICU 2 weeks after onset ALF
5	ALF—survived	2nd trimester	See comments	TDF/FTC/EFV	639		No ARVs from day 1 admission, ALF on day 5, restarted ARVs in ICU on day 7
6	No ALF	3rd trimester	On treatment	TDF/FTC/EFV		<20 copies	
7	No ALF	3rd trimester	On treatment	Unknown		<20 copies	
8	No ALF	3rd trimester	On treatment	TDF/AZT/3tc/LPV-r		<20 copies	2nd line regimen ^a
9	No ALF	3rd trimester	Defaulted	TDF/FTC/EFV	329		Restarted on admission before signs ALF
10	No ALF	2nd trimester	Unknown				
11	No ALF	2nd trimester	On treatment	TDF/3TC/EFV			
12	No ALF	1st trimester	Unknown				Started in 2016, lost to follow up
13	No ALF	3rd trimester	On treatment	TDF/FTC/EFV	559	<20 copies	
14	No ALF	3rd trimester	On treatment	TDF/3TC/AZT/ATVr		<20 copies	
15	No ALF	3rd trimester	Unknown			<20 copies	
16	No ALF	3rd trimester	On treatment	TDF/FTC/EFV	600	<20 copies	

Note: All available data is presented.

Abbreviations: 3TC, lamivudine; ALF, acute liver failure; ARV, antiretroviral; ATVr, atazanavir/ritonavir; AZT, zidovudine; EFV, efavirenz; ICU, intensive care unit; LPV-r, lopinavir/ritonavir; N/A not applicable; TDF, tenofovir.

^aNo recent amendments in drug regimen.

fatality rate, as well as a high fetal case fatality rate. Women who were HIV positive seemed to be more frequently infected with HEV, although not statistically significant. Also HIV infected women appeared to have a better outcome, especially when on ART.

To our knowledge, this is the first cohort reporting acute HEV in pregnancy caused by genotype 2. Our high maternal case fatality rate corresponds with the available literature for genotype 1, as well as the more severe outcome among women in the third trimester and a high mortality rate among women who develop ALF.^{5,20} A systematic review and meta-analysis performed by Jin et al, identified a CFR of 21%, reporting on 3968 pregnancies from both community-based and facility based studies, whereas Berglov et al, identified a CFR of 26%, reporting on 1338 pregnancies from facility-based studies only.^{5,20} It's important to realize, even though most review articles present CFR for genotype 1 and 2 combined, data regarding pregnancy outcomes of genotype 2 are actually scarce as genotype 1 is far more prevalent, especially in Asia.^{2,5,6,20-22} Besides Namibia, genotype 2 has only been identified in Mexico, Chad, Nigeria, Burkina Faso and Central African Republic.²²⁻²⁴ Berglov et al²⁰ solely included studies from areas with genotype 1. Jin et al included only one report from an African country where genotype 2 was prevalent, namely Central African Republic, reporting on seven pregnant women with acute HEV, of which one died.²⁵ We were able to identify one additional study from Chad, reporting on four pregnant women with acute HEV, of whom two died.²⁶

Our fetal outcome also corresponds with the fetal outcome identified in cohorts reporting on genotype 1. The review of Berglov included miscarriage in the intra-uterine stillbirth rate and identified a stillbirth rate of 33% and a neonatal CFR of 8%.²⁰ Jin et al⁵ identified a fetal case fatality rate of 34%, but it is unclear whether miscarriages were included in their definition. Berglov et al²⁰ reported a similar high premature birth rate to ours of 52%. There was no premature birth rate available in the report of Jin et al⁵ We did not

test for vertical transmission in our cohort. Berglov et al reported a vertical transmission rate ranging from 28% to 79%, based on the findings of five studies.²⁰

This is one of the first cohorts reporting on the outcome of pregnant women with HIV and acute HEV. The literature is scarce regarding the clinical impact of HIV/HEV co-infection in pregnant women, as in most of the areas with outbreaks of genotype 1 and 2 there was a low HIV prevalence. Firstly, we identified a slightly higher HIV prevalence in our cohort, compared to the general pregnant population, although not statistically significant. This finding may suggest that HIV positive women are more easily infected by HEV. For all genotypes, the literature is conflicting on whether or not there is a higher seroprevalence of HEV among people with HIV.^{12,13} We found three reports from other African countries. Only in the report from Gabon, a slightly higher seroprevalence was reported among 183 asymptomatic HIV positive pregnant women, as 7% were IgG positive for HEV, compared with 5% of their control group.²⁷ In a Ethiopian cohort with 386 asymptomatic pregnant women, 31.6% were IgG positive and two women were IgM positive. Only 18 women were HIV positive and HEV prevalence did not differ between both groups.²⁸ In the Central African Republic, they found a seroprevalence of 68% among 200 HIV positive adults, which was comparable to the general population.²⁸ Secondly, in our cohort of HIV infected women, in particular those receiving ART, appeared to be at lower risk of a severe clinical course including developing ALF. Although this finding needs to be interpreted with caution because of the small numbers, it is an interesting observation as, with most infections among HIV infected individuals, a more severe outcome could be anticipated. Possible mechanisms contributing to our observations are a reduced immune response, resulting in a mitigated level of hepatitis or a direct effect of the antiretroviral therapy against HEV. Among the eight women on ART there were

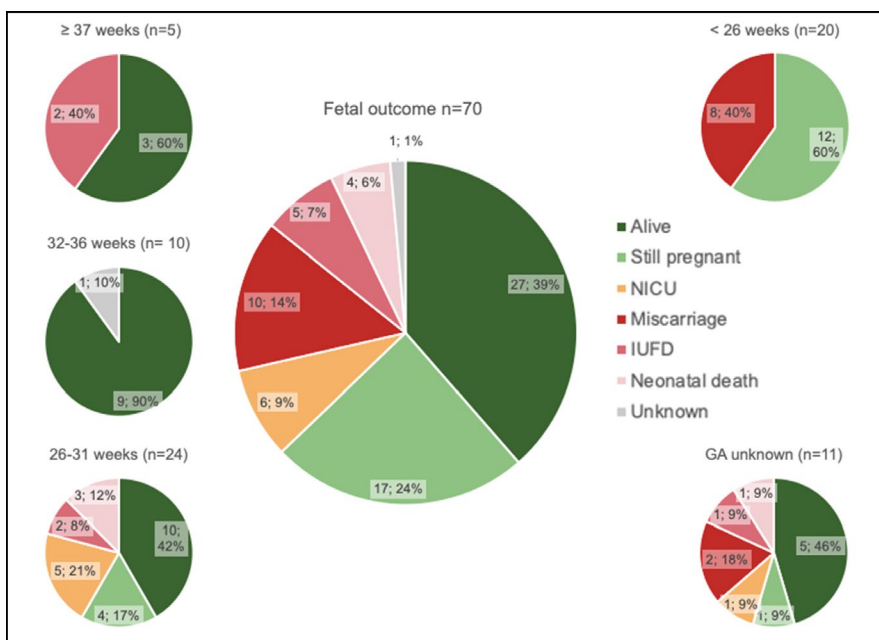


FIGURE 1 Fetal outcome according to gestational age. Largest pie chart presents fetal outcome of the complete cohort. Smaller pie charts present fetal outcome based on gestational age at end of pregnancy. One woman died while still pregnant, fetal outcome in this woman was counted as intra-uterine fetal death. GA, gestational age; IUFD, intra-uterine fetal death; NICU, neonatal intensive care unit

four different drug regimens and therefore we could not further assess the potential protective role of individual ART drugs. Also the duration of pregnancy could not explain this finding as the number of women in the third trimester appeared to be similar for both HIV positive and negative women. Furthermore, a similar trend of a lower HIV prevalence among women with ALF compared to no ALF was identified, when analysing data of women in the third trimester only. To our knowledge, there are no studies available reporting the outcome of pregnant women with acute HEV comparing HIV infected and non-infected women. However, a recent large meta-analysis revealed that ongoing chronic HEV was seen significantly less frequently among HIV infected adults in comparison to transplant recipients, which also suggests that HIV infected adults tend to clear the HEV virus more easily compared to those who are not infected.²⁹

We identified a trend of higher elevated serum transaminases for women with ALF compared to women without ALF, which was not significant and there was a very wide range for these parameters. This is most likely explained by a large variation in condition on admission of the women. While some women presented asymptomatic, others presented after the onset of signs of acute liver failure and a few women only presented in the terminal phase when serum transaminases are decreasing again.

The hepatitis E outbreak had a significant impact on the limited resources of the public healthcare system of Namibia. There were only 14 ICU beds available in the hospital complex in the capital, serving the entire population. A woman with hepatic encephalopathy because of HEV often needed ventilatory support for two to three weeks. Since the start of the outbreak on average one to two ICU beds have been occupied by a young woman with HEV. This increased demand on an already overburdened ICU resulted in more referrals to ICUs of private institutions, resulting in high costs for the Ministry of Health. Similar problems were seen at the neonatal ICU, because of the high frequency of extreme premature birth of HEV infected women. Lastly, the frequent loss of a young woman and unavailability of an effective treatment had an enormous impact on the mental well-being of our staff. The number of maternal deaths has nearly doubled since the start of the outbreak. One of the consultants stated: 'it feels like the HIV era, when we could only hope for the best'.

In our facility we experienced challenges with providing good care to the HEV patients, because of unfamiliarity with the disease, fear of transmission and lack of resources. Especially at the start of the epidemic, several women were misdiagnosed with alcohol intoxication when they presented with hepatic encephalopathy. Others were brought in by the police, accused of performing an illegal abortion when they had a spontaneous premature birth at home. Furthermore, out of fear for transmission, observations were not always done as requested and subsequently deterioration was noted at a late stage. As a result of limited availability of glucose strips, diagnosis of hypoglycaemia was in some cases delayed until clinical symptoms were present. We feel glucose monitoring is essential for all pregnant women with acute HEV,

as hypoglycaemia was often the first sign of the progression towards acute liver failure. To improve care, healthcare workers working in regions affected by the HEV outbreak, were trained in the management of pregnant women with jaundice. This was through video conferencing and sharing management guidelines, which resulted in the provision of better care.

Our study has several limitations. Firstly, there might have been selection bias as hospitalized women were included only. We identified additional patients through our severe morbidity and mortality registry and it is highly likely that the true case fatality rate might be lower. Secondly, our cohort was small and because of the retrospective design some important data, such as HIV status of two women or ART regimen of four women, were missing. Thirdly, we did not determine the HEV genotype or subtype in our cohort, while genotype 2 has been proven to be the causative agent of the outbreak. Lastly, we did not test for vertical transmission from mother to baby, which may have assisted with the interpretation of our poor fetal outcome. A prospective cohort with larger numbers may have resulted in more answers but was not feasible because of limited resources and the sudden onset of the outbreak.

5 | CONCLUSION

Hepatitis E is a disease with many faces: while sporadic chronic HEV infections in immunosuppressed individuals and extrahepatic manifestations are of main interest in high-income countries, low- and middle-income countries suffer from endemic outbreaks involving large populations causing a high mortality in pregnant women. HEV genotype 2 infections and outcome of pregnancy have not been studied in detail previously. This retrospective study shows a mortality rate of almost 20% caused by an ongoing HEV genotype 2 outbreak in Namibia, which is similar to outbreaks with genotype 1. For the first time it was possible to study a potential role of underlying HIV infection and ART in pregnant women threatened by HEV infection. Despite the total numbers being low, it is surprising that HIV infected women in particular those on ART, seem to be less likely to develop acute liver failure in contrast with non-HIV infected pregnant women. These data for the first time indicate that underlying HIV infection or the ART itself might attenuate the severity of HEV genotype 2 infections in pregnant women. More research is urgently needed to confirm or refute this phenomenon in larger cohorts. Understanding the underlying mechanism may potentially lead to treatment options to alter the often fatal outcome of this disease among pregnant women.

ETHICS

This study was reviewed and approved by the research unit of the Namibian Ministry of Health and Social Services. All data were collected from medical records, de-identified and study inclusion did

not have any effect on clinical management. Therefore, the need for individual informed consent was waived. Ref 17/3/3 SBM.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

All available data are presented in the manuscript and tables.

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REFERENCES

- Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology*. 2012;55:988-997.
- Hakim MS, Wang W, Bramer WM, et al. The global burden of hepatitis E outbreaks: a systematic review. *Liver Int*. 2017;37:19-31.
- World Health Organization. *The Global Prevalence of Hepatitis E Virus Infection and Susceptibility: A Systematic Review*. World Health Organization. <https://apps.who.int/iris/handle/10665/70513>. Accessed January 13, 2020.
- Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. *Lancet*. 2012;379:2477-2488.
- Jin H, Zhao Y, Zhang X, Wang B, Liu P. Case-fatality risk of pregnant women with acute viral hepatitis type E: a systematic review and meta-analysis. *Epidemiol Infect*. 2016;144:2098-2106.
- Perez-Gracia MT, Suay-Garcia B, Mateos-Lindemann ML. Hepatitis E and pregnancy: current state. *Rev Med Virol*. 2017;27:e1929.
- World Health Organization. Hepatitis E vaccine: WHO position paper, May 2015. *Wkly Epidemiol Rec*. 2015;90:185-200.
- Nishiyama T, Kobayashi T, Jirintai S, et al. Screening of novel drugs for inhibiting hepatitis E virus replication. *J Virol Methods*. 2019;270:1-11.
- Ministry of Health and Social Services. *Outbreak of Hepatitis E Virus (HEV) in Namibia, Situation Report (SITREP No. 64)*. Ministry of Health and Social Services. <https://www.afro.who.int/sites/default/files/2019-08/National%20SITREP%2064%20on%20Hepatitis%20E%20%20outbreak%20Final.pdf>. Accessed January 19, 2020.
- National Maternal Death, Near Miss, Stillbirth and Neonatal Death Review Committee. *Report on the Confidential Enquiry into Maternal Deaths 1 April 2018 to 31 March 2019 and Near Miss 1 October 2018 to 31 March 2019*. Ministry of Health and Social Services. In press.
- Ministry of Health and Social Services. *Namibia Population-Based HIV Impact Assessment NAMPHIA 2017*. Ministry of Health and Social Services; 2018. <https://phia.icap.columbia.edu/countries/namibia/>. Accessed January 27, 2020.
- Debes JD, Pisano MB, Lotto M, Re V. Hepatitis E virus infection in the HIV-positive patient. *J Clin Virol*. 2016;80:102-106.
- Krain LJ, Nelson KE, Labrique AB. Host immune status and response to hepatitis E virus infection. *Clin Microbiol Rev*. 2014;27:139-165.
- Isaacson M, Freaun J, He J, Seriwatana J, Innis BL. An outbreak of hepatitis E in Northern Namibia, 1983. *Am J Trop Med Hyg*. 2000;62:619-625.
- Maila HT, Bowyer SM, Swanepoel R. Identification of a new strain of hepatitis E virus from an outbreak in Namibia in 1995. *J Gen Virol*. 2004;85:89-95.
- Ministry of Health and Social Services. *National Guidelines for Antiretroviral Therapy*, 5th Edition. Ministry of Health and Social Services; 2016. <https://www.namhivociety.org/resources-docs>. Accessed January 27, 2020.
- Heemelaar S, Josef M, Diener Z, et al. Maternal near-miss surveillance, Namibia. *Bull World Health Organ*. 2020;98:548-557.
- Heemelaar S, Kabongo L, Ithindi T, et al. Measuring maternal near-miss in a middle-income country: assessing the use of WHO and sub-Saharan Africa maternal near-miss criteria in Namibia. *Glob Health Action*. 2019;12:1646036.
- European Association for the Study of the Liver. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. *J Hepatol*. 2017;66:1047-1081.
- Berglov A, Hallager S, Weis N. Hepatitis E during pregnancy: maternal and foetal case-fatality rates and adverse outcomes—a systematic review. *J Viral Hepat*. 2019;26:1240-1248.
- Hartl J, Wehmeyer MH, Pischke S. Acute hepatitis E: two sides of the same coin. *Viruses*. 2016;8:299.
- Aggarwal R, Goel A. Natural history, clinical manifestations, and pathogenesis of hepatitis E virus genotype 1 and 2 infections. *Cold Spring Harb Perspect Med*. 2019;9:a032136.
- Dimeglio C, Kania D, Mantono JM, et al. Hepatitis E virus infections among patients with acute febrile jaundice in Burkina Faso. *Viruses*. 2019;11:554.
- Kim JH, Nelson KE, Panzner U, Kasture Y, Labrique AB, Wierzb TF. A systematic review of the epidemiology of hepatitis E virus in Africa. *BMC Infect Dis*. 2014;14:308.
- Goumba CM, Yandoko-Nakoune ER, Komas NP. A fatal case of acute hepatitis E among pregnant women, Central African Republic. *BMC Res Notes*. 2010;3:103.
- Coursaget P, Buisson Y, N'Gawara MN, Van Cuyck-Gandre H, Roue R. Role of hepatitis E virus in sporadic cases of acute and fulminant hepatitis in an endemic area (Chad). *Am J Trop Med Hyg*. 1998;58:330-334.
- Caron M, Bouscaillou J, Kazanji M. Acute risk for hepatitis E virus infection among HIV-1-positive pregnant women in central Africa. *Virol J*. 2012;9:254.
- Demi Sibiro OA, Manirakiza A, Komas NP. Seroprevalence of hepatitis E virus infection among people living with HIV in the Central African Republic. *Open Forum Infect Dis*. 2018;5:ofy307.
- Buescher G, Ozga AK, Lorenz E, et al. Hepatitis E seroprevalence and viremia rate in immunocompromised patients: a systematic review and meta-analysis. *Liver Int*. 2021;41:449-455

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