



Fetomaternal outcomes in pregnant women with hepatitis E infection; still an important fetomaternal killer with an unresolved mystery of increased virulence in pregnancy

Hepatit E enfeksiyonu olan gebe kadınlarda fetomaternal prognozlar; halen önemli bir fetomaternal öldürücü hastalık ve çözümlenmemiş bir gizem olarak gebelikte virülans artışı

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Abstract

Objective: Hepatitis is a prevalent infection in developing countries. While hepatitis B and C are deepening their roots in the developed world, hepatitis A and E are common in the developing world. The uniqueness of hepatitis is in its transformation from a relatively self-limiting disease in the non-pregnant state, to a highly virulent disease during pregnancy.

Materials and Methods: This retrospective observational study was conducted in the Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, for a period of six months from June 2016 to November 2016 [probably during an endemic peak of hepatitis E virus (HEV)] to observe the clinical outcomes in HEV-infected pregnant women.

Results: A total of 32 anti-HEV immunoglobulin M-positive pregnant women were included, and fetomaternal outcomes were analyzed. Hepatitis E positivity was significantly associated with maternal mortality, intrauterine demise with prematurity, and premature rupture of membranes was the most common fetal complication noted.

Conclusion: The difference in extent of virulence of infection and variations in maternal morbidity, mortality, and rates of intrauterine demise, signify the presence of some factors that play a role and need to be further studied and evaluated.

Keywords: Encephalopathy, hepatitis B, hepatitis E, jaundice, pregnancy

Öz

Amaç: Hepatit, gelişmekte olan ülkelerde sık görülen bir enfeksiyondur. Hepatit B ve C, köklerini gelişmiş dünyada derinleştirirken, hepatit A ve E gelişmekte olan dünyada sık görülmektedir. Hepatitin kendine özgü özelliği, gebelik olmayan durumda nispeten kendi kendini sınırlayan bir hastalıktan, gebelik esnasında bir şekilde yüksek düzeyde virülan bir hastalığa dönüşmesidir.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışma, Haziran 2016 ile Kasım 2016 tarihleri arasında altı aylık bir sürede [muhtemelen hepatit E virüsünün (HEV) endemik olarak pik yaptığı dönemde] King George Tıp Üniversitesi (Lucknow), Kadın ve Doğum Hastalıkları Anabilim Dalı'nda, HEV ile enfekte olmuş gebe kadınlarda klinik prognozları gözlemek üzere yürütülmüştür.

Bulgular: Toplam 32 anti-HEV immünoglobulin M-pozitif gebe kadın çalışmaya dahil edilmiştir ve fetomaternal prognozlar analiz edilmiştir. Hepatit E pozitifliği, maternal mortalite ile anlamlı derecede ilişkili bulunmuştur ve en sık belirlenen fetal komplikasyonlar prematürite ile birlikte intrauterin ölüm ve erken membran rüptürü olmuştur.

Sonuç: Enfeksiyon virülansının derecesinde ve maternal morbidite, mortalite ve intrauterin ölüm oranlarında farklılıklar, etkili olabilecek ve daha fazla incelenmesi ve değerlendirilmesi gereken bazı faktörlere işaret etmektedir.

Anahtar Kelimeler: Ansefalopati, hepatit B, hepatit E, sarılık, gebelik

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PRECIS: Hepatitis E in pregnancy is a virulent disease with high fetal and maternal morbidity and mortality. The burden of the disease can be reduced by providing better sanitary services and clean drinking water to pregnant women.

Introduction

Jaundice in pregnancy is a known high-risk factor that increases fetomaternal morbidity and mortality. While hepatitis B and C are deepening their roots in the developed world, hepatitis A and E are still more common in the developing world. The uniqueness of hepatitis E lies in its transformation from a relatively self-limiting disease in the non-pregnant state to a highly virulent disease during pregnancy. Hepatitis E virus (HEV) belongs to genus Hepevirus and family Hepeviridae. The RNA genome remains enclosed within a capsid composed of one or possibly two proteins, but many questions remain regarding its antigenicity.

Endemics usually occur during the rainy season. Once ingested, the virus first infects the liver followed by viremia and shedding in stool. Liver injury coincides with an elevation of transaminases and the appearance of anti-HEV immunoglobulin (Ig) M. The mechanisms behind its aggressive course during pregnancy are still not clearly understood. Clinical presentation varies from asymptomatic infection to anicteric, icteric, and fulminant hepatitis. Common presenting symptoms include yellowing of the eye and urine, fever, chills, anorexia, nausea, and abdominal pain. Aminotransferases are markedly elevated and may precede the onset of symptoms. Unlike hepatitis B virus (HBV) and hepatitis C virus (HCV), HEV infections are not known to cause cirrhosis or hepatocellular carcinoma.

Pregnant women are more susceptible to infection by HEV and progression to fulminant hepatic failure with high mortality rates and preterm deliveries. The disease is amenable to being prevented by a better sanitation check because the virus has a feco-oral route of transmission.

The present study was planned to evaluate the extent of maternal and fetal morbidity and mortality encountered due to hepatitis E in a tertiary care centre in North India.

Materials and Methods

This retrospective observational study was conducted in the Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, India, over a period of six months from June 2016 to November 2016, the endemic season for hepatitis E. All women with jaundice or history of jaundice in the present pregnancy who delivered during that period were recruited in the study. Jaundice was diagnosed by physical examination but a confirmation was made using liver function tests. The prevalence of jaundice in pregnancy was calculated along with percentages of hepatitis A, hepatitis B, hepatitis C positivity and hepatic encephalopathy. Hepatitis B and C positivity was diagnosed using and enzyme-linked immunosorbent assay and hepatitis A and E were confirmed through IgM positivity. Maternal and fetal outcomes were also

noted from the labor registers and delivery records. The study was reviewed and given clearance by the institutional ethics committee.

Results

Total number of women who delivered during this six-month period was 3692, 177 (4.7%) of whom had jaundice at the time of delivery or during the antenatal period. The women with jaundice were studied in detail and data were classified patients who were HBV positive, hepatitis A virus (HAV) positive, HCV positive, HEV positive, and those who did not have positive viral markers but had jaundice due to other causes such as severe preeclampsia, sepsis, typhoid, dengue or no definite cause. The women who delivered were further classified by their age, antenatal care and registration, period of gestation at delivery, mode of delivery, antepartum or intrapartum fetal demise, preterm premature rupture of membranes, hepatic encephalopathy, and derangement in liver function test, platelets, and coagulation profile. The mean period of gestation at the time of onset of jaundice was 31.7 ± 7.3 weeks.

The age of the patients ranged between 20-38 years with a mean age of 25 years. Table 1 shows the different causes of jaundice encountered in our study. The mode of delivery and fetomaternal outcomes were recorded as shown in Tables 2 and 3. A detailed description of the hepatitis E-positive pregnant women is presented in Table 4. About 90% of preterm deliveries were spontaneous, and 10% were medically induced due to comorbid indications.

Table 1. Different types of jaundice noticed in pregnant women

Total cases of jaundice	n=177	
Hepatitis B	54	30.5%
Hepatitis C	15	8.4%
Hepatitis E	32	18%
Hepatitis A	8	0.4%
Jaundice due to causes other than viral hepatitis	68	38%

Table 2. Mode of delivery in patients with jaundice in pregnancy

	HBV	HCV	HAV	HEV	Others
Total	54	15	8	32	68
LSCS	14	3	1	4	16
Vaginal	36	11	7	28	51
Instrumental	4	1	0	0	1

HBV: Hepatitis B virus, HCV: Hepatitis C virus, HAV: Hepatitis A virus, HEV: Hepatitis E virus, LSCS: Lower segment cesarean section

Discussion

Viral hepatitis is one of the most common causes of jaundice encountered during pregnancy. Amongst all types of viral hepatitis, hepatitis E causes the most damage and is most prevalent in Asia and Africa⁽¹⁾. The prevalence of the disease in the developed world is less and the difference is remarkable. Lachish et al.⁽²⁾ in a 10-year retrospective analysis found only fifteen pregnant women infected with HEV in Israel. Five (33%) patients in their series resulted in fulminant hepatitis, and two patients underwent urgent liver transplantation. They had no mortality among the mothers and fetuses, even in cases that resulted in fulminant liver failure. Other industrialized countries also rarely encounter autochthonous cases of hepatitis E in pregnancy⁽³⁾. We should realize that the scenario in developing countries like India, Pakistan⁽⁴⁾ and Bangladesh⁽⁵⁾ needs to be identified where both prevalence, morbidity, and mortality is high, and advanced modalities of treatment such as liver transplantation are not freely available. The high prevalence is also a constant threat for pregnant women travelling from industrialized countries⁽⁶⁾.

Disease outbreaks have shown to suddenly increase the number of maternal deaths as reported by Gurley et al.⁽⁷⁾ who reported that a sudden increase in jaundice deaths due to fulminant liver failure in pregnancy was retrospectively investigated and anti-HEV IgM positivity was seen in the neighbours of those who died. An accidental sewage contamination of municipal water led to maternal deaths, increased miscarriages, and perinatal mortality. Contrary to its relatively benign course in the non-pregnant state, the infection takes a significantly virulent turn during pregnancy. Systematic reviews and meta-analyses have shown

that patients in later gestations, particularly in the third trimester of pregnancy with HEV positivity or with fulminant hepatic failure, were significantly associated ($p < 0.05$) with maternal mortality and intrauterine fetal death (27.0%)⁽⁸⁾.

HEV is chiefly an enterically transmitted virus, but other modes of transmission have also been proposed including person-to-person transmission, blood, and transplacental transmission⁽⁹⁾. Transplacental transmission is probably the cause behind the high incidence of abortion, preterm labor, and intrauterine demise associated with the disease. Interestingly, HEV replication has also been reported to occur in extra-hepatic sites such as the placenta⁽¹⁰⁾.

Various Indian studies have confirmed the deadly nature and grievous impact of hepatitis E infection on maternal and fetal life. In our study period, owing to an endemic, 32 patients delivered who were positive with a documented report of anti-HEV IgM positivity. Of these, the majority (78%) had not received adequate antenatal care hospital prior to registration at our hospital. The majority of women with jaundice, including those who were hepatitis E-positive, delivered vaginally. Amongst the pregnant women affected by hepatitis E, 12 (37.5%) presented with intrauterine demise in the antepartum period, and 2 (6.2%) had an intrapartum intrauterine demise. The rate of preterm delivery was 71.9%, and 28.1% delivered before 28 weeks. Seven (21.8%) women resulted in hepatic encephalopathy, and 31.2% had a deranged coagulogram. There were seven (21.8%) maternal deaths. All these numbers were significantly higher than in other types of viral hepatitis. Fetomaternal outcomes were significantly better with HBV, HCV, and HAV hepatitis compared with HEV, as shown in Table 3.

Table 3. Distribution of different types of jaundice with fetomaternal outcomes

	HBV	HCV	HAV	HEV	Others
Total	54	15	8	32	68
Term	41	10	6	9	15
Preterm	13	5	2	23	53
PPROM	2 (3.7%)	0	1 (12.5%)	9 (28.1%)	2 (2.9%)
Preterm <28 weeks	1 (1.8%)	0	1 (12.5%)	9 (28.1%)	14 (20.5%)
Fetal outcomes					
Live births	49	13	6	18	42
Still births	5	2	2	14	26
Antepartum	3 (5.5%)	1 (6.6%)	2 (25%)	12 (37.5%)	18 (26.4%)
Intrapartum	2 (3.7%)	1 (6.6%)	0	2 (6.2%)	8 (11.7%)
Maternal outcome					
Maternal death	0	1 (6.6%)	0	7 (21.8%)	11 (16.1%)
HE	0	0	0	7 (21.8%)	14 (20.5%)
Coagulopathy	0	0	0	10 (31.2%)	10 (14.7%)

HBV: Hepatitis B virus, HCV: Hepatitis C virus, HAV: Hepatitis A virus, HEV: Hepatitis E virus, HE: Hepatic encephalopathy, PPRM: Preterm premature rupture of membranes

Table 4. Details of hepatitis E infected cases

Sn	POG at jaundice	Bil (d)	SGPT	SGOT	Platelet	Period of gestation	Mode of delivery	Fetal outcome	Maternal outcome
1	33 weeks	15	1670	1500	50.000	Preterm	Vaginal	Stillborn	Expired
2	35 weeks	12	1000	1000	30.000	Preterm	Vaginal	Stillborn	Normal
3	28 weeks 2 days	11	1100	1200	55.000	Preterm	Vaginal	Stillborn	Expired
4	31 weeks	18	3000	1900	25.000	Preterm	Vaginal	Stillborn	Expired
5	29 weeks 6 days	6	500	567	1 lacs	Preterm	Vaginal	Stillborn	Normal
6	28 weeks 2 days	4.5	28	55	90.000	Preterm	Vaginal	Stillborn	Normal
7	24 weeks 5 days	6.8	550	300	1.7 lacs	Term	Vaginal	Normal	Normal
8	28 weeks 3 days	12	2400	1542	2 lacs	Preterm	Vaginal	Stillborn	Expired
9	32 weeks 1 day	14	1158	1657	60.000	Preterm	Vaginal	Stillborn	Normal
10	27 weeks 2 days	1.7	34	33	2 lacs	Preterm	Vaginal	Stillborn	Normal
11	24 weeks 6 days	10	1009	493	30.000	Preterm	Vaginal	Stillborn	Expired
12	36 weeks 3 days	8.7	251	86	2 lacs	Preterm	Vaginal	Normal	Normal
13	33 weeks 6 days	6.7	281	129	2 lacs	Preterm	Vaginal	Normal	Normal
14	35 weeks 1 day	4.8	70	88	1.8 lacs	Preterm	Vaginal	Normal	Normal
15	33 weeks	18	2500	2000	250.000	Preterm	Vaginal	Stillborn	Expired
16	39 weeks 6 days	3	300	260	2 lacs	Term	Vaginal	Normal	Normal
17	24 weeks	20	17	63	30.300	Preterm	Vaginal	Stillborn	Expired
18	28 weeks	6	150	177	1.4 lacs	Preterm	Vaginal	Normal	Normal
19	Term	4	40	45	1.5 lacs	Term	Vaginal	Normal	Normal
20	31 weeks	0.4	41	72	1.9 lacs	Preterm	LSCS	Normal	Normal
21	38 weeks 4 days	7	550	400	90.000	Term	Vaginal	Normal	Normal
22	39 weeks 2 days	9	282	384	98.000	Term	LSCS	Normal	Normal
23	26 weeks 2 days	7.9	653	598	2 lacs	Preterm	Vaginal	Stillborn	Normal
24	37 weeks	7.3	249	99	1 lacs	Term	Vaginal	Normal	Normal
25	38 weeks 2 days	3	90	99	1.7 lacs	Term	Vaginal	Normal	Normal
26	35 weeks	5	115	150	1.2 lacs	Term	Vaginal	Normal	Normal
27	34 weeks 4 days	7	800	779	1 lacs	Preterm	Vaginal	Stillborn	Normal
28	40 weeks 1 days	6	90	88	2 lacs	Term	Vaginal	Normal	Normal
29	36 weeks 5 days	5	96	67	1.1 lacs	Preterm	LSCS	Normal	Normal
30	35 weeks	7	100	99	1 lacs	Term	LSCS	Normal	Normal
31	33 weeks 5 days	8	200	198	1.2 lacs	Preterm	Vaginal	Normal	Normal
32	31 weeks	7.8	680	400	1.8 lacs	Preterm	Vaginal	Normal	Normal

POG: Period of gestation, Bil: Bilirubin, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, LSCS: Lower segment cesarean section

On applying the unpaired t-test, we found that adverse fetal outcomes were significantly associated with rising serum bilirubin levels of more than 11 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) of more than 1000 IU/L, and a platelet count of less than 85.000 cells/mm³, and this difference was statistically significant.

Maternal outcomes were also significantly poorer in cases of serum bilirubin of more than 14 mg/dL, SGPT more than 1600, and SGOT more than 1200 and platelets less than 59.000 cells/mm³, as shown in Tables 5 and 6.

Looking at the fetomaternal outcomes at the time of delivery and applying the chi-square test, we found that preterm vaginal delivery had a statistically significant risk of poor fetal outcome,

whereas it was nonsignificant as far as poor maternal outcomes were concerned, as shown in Tables 7 and 8.

Similar poor outcomes have been reported by several authors. Sahai et al.⁽¹¹⁾ reported that viral hepatitis in pregnancy led to high maternal mortality and also fetal wastage, especially if women presented with features of encephalopathy, fulminant hepatic failure, and coagulopathy.

Shinde et al.⁽¹²⁾ reported in their 2-year prospective study that 46.1% of pregnant patients developed encephalopathy compared with 34% in the non-pregnant group. Among the pregnant women, 67.3% survived and 32% died. In the non-pregnant group, most patients survived and only 9% died. This difference was statistically significant (p<0.01). Adverse fetal outcomes were seen in 71.1% of pregnant women with acute

Table 5. Comparison of various parameters with fetal outcome

	Fetal outcome	n	Mean	Standard deviation	p
POG at jaundice	Normal	18	32.8889	9.18694	0.331
	Stillborn	14	30.3000	3.80607	
Bil (d)	Normal	18	5.8611	2.23347	0.001*
	Stillborn	14	11.2214	5.44669	
SGPT	Normal	18	229.72	189.474	<0.001*
	Stillborn	14	1133.50	948.646	
SGOT	Normal	18	174.50	121.416	<0.001*
	Stillborn	14	956.21	688.345	
Platelet (in lacs)	Normal	18	1.5100	0.41292	0.002*
	Stillborn	14	0.8536	0.67467	

Applied unpaired t-test for significance, *Significant

POG: Period of gestation, Bil: Bilirubin, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase

Table 6. Comparison of various parameters with maternal outcome

	Maternal outcome	n	Mean	Standard deviation	p
POG at jaundice	Normal	25	32.5640	7.95811	0.247
	Expired	7	28.8714	3.68271	
Bil (d)	Normal	25	6.3440	2.94067	<0.001*
	Expired	7	14.8571	3.93398	
SGPT	Normal	25	332.32	320.066	<0.001*
	Expired	7	1670.86	1039.625	
SGOT	Normal	25	313.20	375.392	<0.001*
	Expired	7	1242.57	720.751	
Platelet (in lacs)	Normal	25	1.3992	0.51057	0.001*
	Expired	7	0.5929	0.63208	

Applied unpaired t-test for significance, *Significant

POG: Period of gestation, Bil: Bilirubin, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase

hepatitis E, including pre-term delivery in 23%, stillbirth in 23%, abortion in 3.8%, and intrauterine fetal death in 21.1% of patients.

Sultana and Humayun⁽¹³⁾ reported in their two years' experience of 25 patients who had acute hepatitis E while one amongst them also had coexistent acute hepatitis A. Twenty-four hepatitis E positive (96%) patients presented in third trimester of pregnancy while one (4%) pregnancy ended in the second trimester as a missed miscarriage. Twenty-one (84%) babies were born alive, 18 (86%) of which were preterm. Perinatal mortality was 26%, which was contributed to by intrauterine deaths and early neonatal deaths in 3 (14%) cases each. In total there were 5 (20%) maternal deaths, 4 (80%) in postpartum period and 1 (20%) in the antepartum period due to fulminant hepatic failure.

A recent six-month study conducted by Singla et al.⁽¹⁴⁾ reported 27 HEV-positive (36%) women amongst a total of 82 women

with jaundice. All five maternal deaths that they reported were not registered anywhere for antenatal care prior to presenting at their hospital and had raised bilirubin of more than 15 mg/dL with deranged coagulograms, encephalopathy, and intrauterine fetal deaths. On analyzing the morbidity data, it was also found that HEV-positive women had poorer outcomes as compared with their hepatitis B surface antigen-positive counterparts. In a 3-year prospective study, Prasad et al.⁽¹⁵⁾ reported 55 symptomatic women who were anti-HEV IgM-positive with maternal mortality of 5% and one antenatal death. Similar to our study, they also found prematurity and preterm rupture of membranes as the most common fetal complication.

In our experience, we found that 56% of women had normal outcomes, whereas the disease turned virulent in the rest with maternal death in 21.8% and fetal demise in 77.7%. What the factors are that govern the virulence of the disease and why virulence is typically increased in pregnant states remain unanswered questions. Bi et al.⁽¹⁶⁾ found that pregnancy serum accelerated HEV replication by suppressing oestrogen receptors and type I interferon in the early stage of infection. A comparison has also been reported between the clinical and subclinical presentation of the disease in pregnancy so as to understand why the disease can sometimes be self-limiting while other times it is life threatening. Several concepts have been studied to look for the cause of heightened disease severity in pregnancy. Ramdasi et al.⁽¹⁷⁾ showed antibody-dependent disease severity and impaired immune response in pregnant women with a differential elevation of cytokines in clinical and subclinical hepatitis E disease. The study by Pal et al.⁽¹⁸⁾ compared immune parameters among pregnant women with acute hepatitis E versus non-pregnant patients with hepatitis E and found reduced production of T-helper 1 (Th1) cytokines and an increase Th2 cytokines in the pregnant HEV group, which indicated a peculiar pathogenesis in pregnancy.

It is thought that a super infection of hepatitis E in patients with hepatitis B worsens liver disease. Huang et al.⁽¹⁹⁾ performed a two-year study to find the incidence of HEV infection among

Table 7. Relating mode and time of delivery with fetal outcome

		Fetal outcome		Total	
		Normal	Stillborn		
Mode	PTVD	6	14	20	
	% Fetal outcome	33.3%	100.0%	62.5%	
	FTVD	8	0	8	
	% Fetal outcome	44.4%	0.0%	25.0%	
	LSCS	4	0	4	
	% Fetal outcome	22.2%	0.0%	12.5%	
Total		Count	18	14	32

Applied χ^2 test for significance, p=0.001 considered significant
 PTVD: Preterm vaginal delivery, FTVD: Full term vaginal delivery, LSCS: Lower segment cesarean section

Table 8. Relating mode and time of delivery with fetal outcome

		Maternal outcome		Total	
		Normal	Expired		
Mode	PTVD	13	7	20	
	% Maternal outcome	52.0%	100.0%	62.5%	
	FTVD	8	0	8	
	% Maternal outcome	32.0%	0.0%	25.0%	
	LSCS	4	0	4	
	% Maternal outcome	16.0%	0.0%	12.5%	
Total		Total	25	7	32

Applied χ^2 test for significance, p=0.105 considered not significant
 PTVD: Preterm vaginal delivery, FTVD: Full term vaginal delivery, LSCS: Lower segment cesarean section

HBV-infected pregnant women and found that HEV infection was not a common occurrence with hepatitis B. None of their 391 HBV-infected patients were anti-HEV IgM-positive. We also had only one patient with both HBV and HEV positivity; we found the patient did not have a very different course than others.

Vertical transmission and intra-family transmission has also been studied and is variously reported in literature. It was reported as low by Gu et al.⁽²⁰⁾, whereas Krain et al.⁽²¹⁾ have raised doubts about it due to inadequate research in the area of vertical transmission of HEV from mother to child.

The present study illuminates various points including the immense burden of disease in peak season, the extent of virulence in the form of fetomaternal life, and the uncertainty of disease course. The strength of the study is in the large number of test-positive HEV-positive pregnant women whose outcomes were evaluated.

Study Limitations

The weaknesses of the study were the non-evaluation of virus positivity in neonates, plus the non-availability of immediate liver transplant for women with fulminant liver failure who might have been saved. Also, only symptomatic HEV-infected women were studied and asymptomatic women were missed because universal testing was not possible even in the endemic season due to resource constraints. The reasons of varied disease nature is a topic of future research, also it is important to time delivery after a test is determined positive because of the high incidence of intrauterine demise and prematurity.

Conclusion

Hepatitis E is a deadly fetomaternal disease. The disease picture shows immense variation from patient to patient, which requires further research so as to better ascertain which factors play a role. It accounts for a significant number of deaths and increases the maternal mortality rate of the country.

The World Health Organization (WHO) also recognizes the burden of the disease. Due to the lack of sufficient information on safety, immunogenicity, and efficacy in pregnant women, the present position statement of the WHO does not recommend use of vaccines in pregnant women, or children aged <16 years⁽²²⁾.

Unlike other diseases such as HIV, it also has a feco-oral route of transmission and hence the disease burden can be lessened by ensuring better sanitation and provision of clean drinking water for pregnant women.

Ethics

Ethics Committee Approval: The study was approved by the King George's Medical University but the institution committee did not mandate an approval number because it was a retrospective analysis.

Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.D., N.K., Concept: A.A., N.K., Design: N.K., V.D., Data Collection or Processing: S.A., N.K., Analysis or Interpretation: N.K., A.A., Literature Search: S.A., A.P., Writing: N.K., A.A.

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