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Effectiveness of prophylaxis for hepatitis B in infants born to mothers serologically positive in Benghazi Medical Center.

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Highlights

- **Libya is an area of intermediate endemicity for Hepatitis-B**
- **Hepatitis B vaccination and hepatitis B immunoglobulin can reduce the risk of chronic hepatitis by up to 90%.**
- **The assessment of the effectiveness of hep. B immune prophylaxis is important to ensure that protection is achieved.**
- **The assessment by testing the titer for hepatitis BS Ag and anti-Hepatitis B antibodies will give an idea regarding the causes of failure of response and try to manage them.**

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ABSTRACT

Background: The seroprevalence of HBs Ag among the general population in Libya was found to be 2.2 %. Libya is therefore considered an area of intermediate endemicity for hepatitis B. vertical transmission is considered as the main route of spread of this infection. Trans placental (intra-uterine) transmission is presumed to cause the minority. Risk factors for transmission of HBV include maternal HBe Ag positivity, HBs Ag titer, and HBV viral load. Active immunization with hepatitis B vaccine (Hep. B vaccine), and hepatitis B immunoglobulin (HBIG) is 85-95% effective in preventing the disease.

The objective of the study: To assess the effectiveness of hepatitis B vaccine and hepatitis B immunoglobulin in the prevention of the Hep. B. virus transmission and to study the factors that affected the immune response of the newborn babies of mothers with hepatitis B positive infection during pregnancy.

Patients & Methods: A longitudinal cross-section study included 40 babies born to mothers with hepatitis B during the period from 1.1.2017 To 1.3.2019 at Benghazi Medical Center. The newborn babies have been immunized with Hepatitis BIG and Hepatitis B vaccine at birth, and further 3 doses of hep. B vaccine and HBIG. Multivariable analyses were done to assess the statistical significance associated with responders and nonresponders to HB immune prophylaxis.

Results: all babies were negative for hepatitis Bs Ag in 40(100%), 35 (88%) their viral load was <2000IU/ml, HBIG and hepatitis B vaccine were administered within the first 12 hours in 37(92.5%) and 35(75%) respectively. A high level of immune response was demonstrated (>10 mlIU/ml) in More than two-thirds (60%) and (63%) of infants at 9 months and 12 months respectively. Birth weight >2.5 kg was significantly associated with immune response >10 mIU/ml, whereas, Maternal viral load, time of administration of HBIG, and hep. B vaccine, gestational age, mode of delivery, type of feeding were statistically not significant.

Conclusion: the study reported that all the newborn babies were negative for hepatitis B sAg after delivery, more than two-thirds of the babies were responders to immune-prophylaxis, and birth weight of >2.5kg was significantly related to high immune-response.

1. Introduction

An estimated 350 million people world wild are infected with hepatitis B virus (HBV), at least 50% acquired their infections either perinatally or in early childhood, especially in countries where HBV is endemic (Alter, 2003). It was attributed to the high rates of HBe Ag positive infections in women of child-bearing age in these parts of the world (Maureen, 2009). The seroprevalence of HBs Ag among the general population in Libya was found to be 2.18% and 2.20% in 2004 and 2005 respectively (Elzouki, 2008). Therefore, Libya is considered as an area of intermediate endemicity for hepatitis B infection (Elzouki, 2008). Perinatal transmission of HBV results in a high frequency of chronic infection and vertical transmission of HBV is considered as the main route of spread of infection in endemic regions. The risk of perinatal transmission is associated with the hepatitis Be Ag status of the mother. If a mother is positive for both hepatitis B surface and e antigen, 70% to 90% of her children become chronically infected (Akhter *et al.*, 1992). Perinatal transmission in the majority of cases occurs at or near the time of birth because of the risks of HBV transmission at delivery from exposure to cervical secretions and maternal blood. Trans placental (intra-uterine) transmission is presumed to cause a minority of transmission of infections. The risk factors for the transmission of

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HBV are maternal HBe Ag positivity, HBs Ag level, and HBV viral load. Infants who were born without immune prophylaxis to HBs Ag positive and HBe Ag positive mothers have a 70% to 90% risk to develop chronic infection of HBV. The risk to develop chronic HBV infection will be reduced to 10-20% if the mother is negative for HBe Ag (Xu *et al*., 2002). Moreover, many studies documented that a maternal HBV viral load above 10^7-10^8 copies/mL (IU/mL), will increase the risk of vertical transmission (Xu *et al*., 2002; Wiseman *et al*., 2009).

In 1984, the advisory committee on immunization practices (ACIP) of the centers for disease control and prevention (CDC) recommended that infants born to HBs Ag-positive women receive post-exposure prophylaxis (Stephen *et al*., 2014). Post-exposure prophylaxis, consisting of hep. B vaccine and HBIG within 12 hours of birth, followed by hep. B vaccine series is 85-95% effective in preventing perinatal transmission (Wong *et al*.,1984; Mast *et al*., 2005). Prevention of perinatal HBV infections is a key priority in controlling HBV transmission. Active vaccination of newborns within 48 h of delivery is very effective. In Libya, the neonatal vaccination program against HBV started in 1993. Later on, age cohorts born in 1991-1992 were vaccinated by the vaccination campaigns in 2005 and 2006 respectively (Mandour *et al*., 2013). The majority of infants with anti-HBS levels >10mlIU/ml within 1-2 months after having received a complete vaccine series are considered protected by immune memory HB through expansion and differentiation of antigen-specific T and B lymphocytes even when anti-HBS levels decline to <10 ml IU/ml over time (Banatvala *et al*., 2000a, 2003b).

2. Aims of the study

2.1. To assess the effectiveness of the hepatitis B vaccine and hepatitis B immunoglobulin in the prevention of the disease by assessing the level of hepatitis B surface antibodies anti-HBs titer and HBs Ag in the newborn.

2.2. To study the factors that affect the immune response of the babies of the mother with hepatitis B (age, mode of delivery, immune prophylaxis, birth weight, gestigenal age, maternal age, and viral load)**.**

3. Patients and Methods

3.1. Design of the study

A longitudinal cross-sectional study was used. All the babies were born to mothers with hepatitis B during the period from 1st Jan.2017 to 1st March .2019 in Benghazi Medical Center (BMC).

3.2. Sampling

All mothers who had been diagnosed to have Hepatitis B infection and confirmed HBs Ag by use of ELISA (Enzyme-Linked Immunosorbent Assay) and PCR (Polymerase chain reaction) and their babies during the mentioned period were included in the study.

3.2.1. Inclusion criteria

The study included all the babies transferred to NICU department at BMC that received the first dose of both HBIG and Hep. B vaccine and can be followed up until the age of 9 and 12 months for investigations.

3.2.2. Exclusion criteria

The study excluded the mothers with HIV and HCV, and the babies who received the first dose of Hep. B vaccine without HBIG. The total number of babies was 111 during that period, 35 refused to involve in the study and some HBIG was not available in the city, another 36 were eliminated because they were not willing to do investigation for their babies. The final sample size was 40 babies included in the study.

3.3. Data collection

The data was collected from mothers by use of a semi-structured interview questionnaire. The interview included: History regarding the Hep. B disease was taken from the mothers, including when the mother was diagnosed to have hepatitis B, family history of contacts including the husband, sibling, whether her family members were vaccinated against hepatitis BV. Requirement of treatment during the pregnancy, mode of delivery and whether the mothers had fed their babies by breast or bottle feeding and the viral load during pregnancy was documented from medical records; the cut-off value was 2000IU/ml(200,000 mIU/ml) as recommended in clinical algorithm done by Centers for disease control and prevention(CDC) and American College of Obstetricians and Gynecologists. Neonatal medical records were used to collect data about the newborn of mothers with a positive history of hepatitis B.

3.4 Follow-up clinic

The babies were immunized with Hepatitis B Immunoglobulin and three doses of hepatitis B, the time of information about the administration was recorded. The mothers with their babies followed up in the neonatal clinic. The investigation for HBs Ag by ELISA and anti-HBs were done at age of 9 and12 months after complete 3 doses of vaccine as recommended now instead of 18 months age which was done previously to assess the level of antibodies for another booster which was the advice for our babies with anti-HBs ≤10 ml IU/ml.

3.5. Data analysis

The data were analyzed by use of statistical packages of scientific survey (SPSS) program version 20 According to their response to the vaccine; babies were divided into respondents >10 mIU/ml and non-responders whose anti-HBs were ≤10 mIU/ml and responders with anti-HBS >10 mIU/ml Statistically significant predictor variables associated with the response to the vaccine were analyzed by use of odd ratio between non-responders and responders, chi-square at 95% degree of precision and use of probability <0.05 as significant level.

3.6. Ethics

Verbal consent was obtained from mothers before participation in the study. The purpose and duration of the study were explained to mothers of participants and participation in the study was voluntary.

3.7. Limitations of the study

- It was a time-consuming study that leads to a high dropped out in the number of cases.
- The test for HBe Ag was unavailable in the medical records of the mothers, and this makes a question whether the cause for all babies was negative was attributed to that all mothers might be negative for HBe Ag.
- Elimination of some babies from the study contributed to HBIG was not available in the country.

4. Results

The present study included forty neonates who were born from 1st of January 2017 till 1st of March 2019 to mothers with HBV infection. This study revealed that; all babies born to hepatitis B mothers were negative for hepatitis Bs Ag 40(100%), 24 (60%) of mothers aged 30 years or more and the mean maternal age was 31.1±5.7 years minimum age 18 years and maximum age 43 years. The current study revealed that 24(60%) of neonates were from Benghazi, 38 (95%) were full-term, 36(90%) had a birth weight ≥of 2.5 kg and 22(55%) were males. The study reported that 20 (50%) of neonates were delivered normally. only 4 (10%) exclusively breastfeed, 27(67.5%) were breast and bottle feed, and 9 (22.5%) were bottle feed. The study indicated that 29 (72.5%) of mothers were diagnosed one year or more, 35(87.5%) their viral load was

<2000IU/ml, and 5(12.5%) their viral load was>2000IU\ml. only 6(15%) mothers received treatment,10 (25%) of family members were infected with HBV, 28(70 %) of family members were vaccinated against HBV, and 20 (50%) their source of infection was due to dental procedure (Table 1).

As registered by an obstetrician in the antenatal follow-up records of the mothers of newborn babies under study 35(88%) of the mothers with viral load <2000 IU/ml, and 5(12.5%) their viral load was >2000IU/ml. The present study revealed that out of 6 (15%) mothers who have received treatment during pregnancy four were with high viral load >2000IU/ml, and two with low viral load was on treatment while 34(85%) of mothers did not receive any antiviral treatment during pregnancy (Table 1).

Table 1

Characteristics of the mothers with HBV infection and their newborn babies

Items	Number	%
Mothers received Treatment:		
Yes	6	15.0
No	34	85.0
Vaccinated family member against HBV:		
Yes	28	70.0
No	12	30.0
Family member with HBV infection:		
Positive	10	25.0
No	30	75.0
Maternal viral load		
≤2000 IU/ml	35	87.5
>2000 IU/ml	5	12.5
Time the neonate received vaccine/hours after birth		
≤12	30	75.0
>12	10	25.0
Time the neonate received HBIG/hours after birth		
≤12	37	92.5
>12	3	7.5
Antibodies at 9 months		
≤10 IU/ml	14	35
>10 IU/ml	24	60
Missing	2	5
Antibodies at one year		
≤10IU/ml	15	37.5
>10 IU/ml	25	62.5
Total	40	100

Hepatitis B immunoglobulin (HBIG)is usually administrated in the neonatal unit immediately after delivery. The present study revealed that 37 (92.5%), and 30 (75%) infants have received HBIG and the first dose of hepatitis B vaccine within the first 12 hours (Fig. 1).

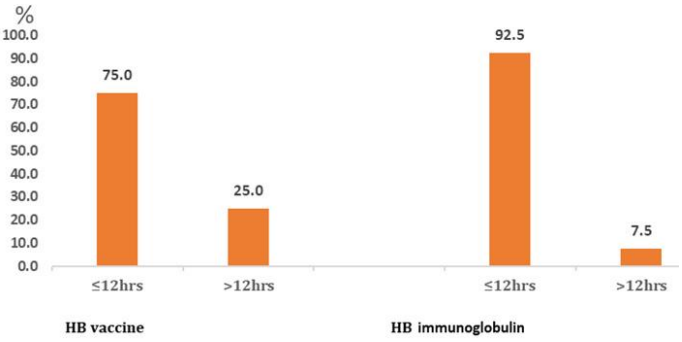

Fig. 1. Time of administration of Hebabtitis B vaccine and Hebatitis immunoglobulin.

The present study reported that >10 mIU/ml HB antibodies were reported in 24 (60%) and 25(63%) of infants at the age of 9months and 12 months respectively. The investigators compare the two groups of infants according to their immune response to HBimmuine prophylaxis. The current study categorised the infants according to antibody levels, into responders (>10 mIU/ml)and non-responders with anti-antibodies (≤10 mIU /ml)at age of 9 months old and at the age of one year (Fig. 2). The present study revealed that the immune response of both responders and non-responders may be related to some factors. The test of significance and odds ratio was used to assess the relationship between an infant's immune response and gender, gestational age, mode of delivery, viral load, time of administration of HBIG, and hep. B .vaccine, type of feeding, and birth weight. The current study revealed a significant relationship between birth weight ≥2.5 kg at age of 9 months and immune response anti-HBs antibodies >10 mIU/ml (OR=1.7 & CI (1.2-2.3) as compared to infants with birth weight ≤2.5 kg, and no significant relations between immune response and the other factors (Table 2).

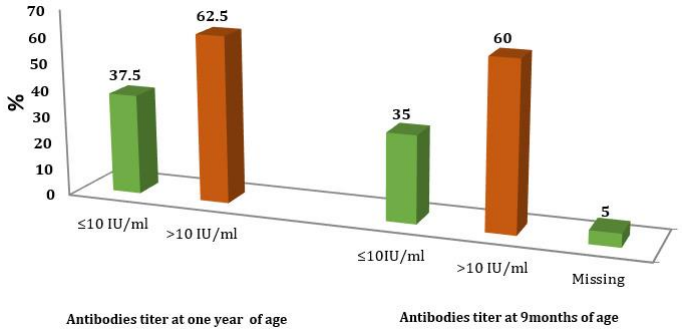

Fig. 2. Anti-HBs levels after immunoprophylaxis against HBV infection.

5. Discussion

The present study reported that the newborn babies were not infected with the hepatitis B virus. as indicated by the negative results of HBs Ag. Similar results were reported in some studies in Iran and Kurdistan (Zahra *et al*., 2016 & Amira *et al*., 2018). In the present study, the mothers were not investigated for HBe Ag, which is one of the risk factors of the transmission of HBV. The negativity of HBsAg and the positivity of anti-HBs both support that the chronic infection was excluded, but did not exclude the transmission of the disease. Because, in acute infection; HBs Ag can be cleared up and resolved by the time of 6 months (we did the investigation after that, anti-HBs will be positive and anti-HB core which helps in the diagnosis of acute infection cannot be detected when vaccination was given. The schedule of immuno-prophylaxis consists of HBIG and the first dose of hep. B vaccine, which should be given within the first 12 hours after birth.

In the present study majority of the motheŕs their age were ≥30 years. The age at which the mothers are exposed more to the procedures that may be risky for hepatitis B infection. It was the age of the highest number in a lot of studies were done (Zahra *et al*., 2016; Sarah *et al*., 2015; Lei Zhang *et al*., 2014), the average age in another two studies was 25-30 years (Stephen *et al*., 2014; Guo *et al*., 2017). In the present study, 95% of newborn babies were full-term and 5% was preterm; its similar to the other countries: USA, China, Iran (Stephen *et al*., 2014; Zahra *et al*., 2016; Sarah *et al*., 2015; Guo *et al*., 2017; Chong *et al*., 2016; Huaibin *et al*., 2011; Yun-Mi *et al*., 2007). The other studies showed no difference in gestational age and prematurity in babies born to mothers with hepatitis B.

In the present study, the majority of newborn babies (90%) with birth weight ≥2.5 kg as in the others (Stephen *et al*., 2014; Zahra *et al*., 2016; Sarah *et al*., 2015; Guo *et al*., 2017; Yun-Mi *et al*., 2007). Two studies reviewed the highest number with the birth weight >3-3.5 kg (Chong *et al*., 2016 & Yun-Mi *et al*., 2007).

Table 2

Relation between certain maternal and infant characteristics and immune response at 9 months and one-year-old babies born to mothers infected with HB

Characteristics	N=38 (2missing)	Antibodies after 9months		N= 40 Antibodies one year	
	Non-responders (≤10 I U/ml) No. (%)		Responders (>10 IU/ml) No. (%)	Non-responders (≤10 I U/ml) No.(%)	Responders (>10 IU/ml) No.(%)
Sex	Male	9(64.3)	13(54.2)	8(53.3)	14(56.0)
	Female	5(35.7)	11 (45.8)	7 (46.7)	11(44.0)
Test of sig.		OR=1.5& CI (0.39-5.9)		OR0.9 & CI (0.25-3.25)	
Birth weight	<2.5kg	0	4(16.7)	2(8)	3(12.0)
	>2.5kg	14 (100)	20(83.3)	13(82)	22(88)
Test of sig.		OR=1.7& CI (1.2-2.3)*		OR=1.2& CI (0.7-7.7)	
Gestational age	Full term	14(100)	23(96)	14(93.3)	24(96.4)
	Preterm	0	1(4.0)	1(6.7)	1(3.9)
Test of sig.		OR=0.13& CI (0.4-0.8)		OR=0.6& CI (0.04-10.0)	
Mode of delivery	Normal	8 (57.1)	10(41.7)	9(60)	11(44)
	CS	6(42.9)	14(58.3)	6 (40)	14 (60.7)
Test of sig.		OR=1.7&CI (0.4-7.3)		OR=4.2&CI (0.90-19.6)	
Maternal age /years	< 30 years	6(42.9)	10(41.7)	5(33.3)	11(44)
	≥ 30 years	8(57.1)	14(58.3)	10(66.7)	14(56)
		OR=1.3 &CI (.33-4.98)		OR=0.64& CI (0.17-2.41)	
Maternal viral load	<2000 IU/ml	11(83.3)	21(88)	12(85.7)	22(89.3)
(Missing1)	>2000 IU/ml	2(16.7)	3(12)	2(14.3)	3(12)
Test of sig.		OR= 0.8 &CI (.11-5. 4)		OR= 0 .81 & CI(0.12-5.59)	
Time received HB vaccine	<12hrs	10(71.4)	21(88)	12(80)	18(72.0)
	≥12 hours	4(28.6)	3(12)	3(20)	7(28.0)
Test of sig.		OR= 0.8&CI (0.2-3.7)		OR=1.6 & CI (0.3-7.2)	
Time received HBIG	<12 hours	14(100)	21(87.5)	15(100)	22(88.0)
	≥12hours	0	3(12.5)	0	3(12.0)
Test of sig.		OR= 0.63 &CI (0.5-0.8)		OR= 0.6& CI (0.5-0.8)	
Type of Feeding:					
Exclusive breastfeeding		1(7)	3(12.5)	1(6.7)	3(12)
Breast and bottle feeding		9(64.2)	18 (75.0)	9(60.0)	18(72.0)
Bottle feeding only		4(28.8)	3(12.5)	5(33.3)	4(16.0)
Test of sig.		X^2_2=1.7&P=0.43		X^2_2=2.04& P= 0.36	
Total		14/38	24/38	15/40	25/40

Significant

In the present study, the babies were delivered equally by cesarean section and vaginally as in most of the studies were done and mentioned here as resources. All these characteristics: gestational age, maternal age, and type of feeding and mode of delivery were not significantly related to immune prophylaxis failure which means (babies were at risk for transmission of hepatitis B infection serologically were HBs Ag positive) as in the studies (Lei Zhang *et al*., 2014; Chong *et al*., 2016; Yun_mi *et al*., 2007).

In the present study, 67.5% of newborn babies were breastfed and bottle-feed, 22% bottle feed, and 10% exclusively breastfeed. Although breastfeeding is still no evidence that is a route of hepatitis B transmission, the mothers were still bottle-fed their babies and avoid breastfeeding, while in the other studies done in China and Iran, most of them were exclusively breastfed (Zahra *et al*., 2016; Guo *et al*., 2017; Chong *et al*., 2016).

According to the obstetrician 88 % of the mothers with viral load <2000IU/ml, and only five mothers (12.5%) their viral load was >2000IU/ml. A similar result was reported, in China, most of the mothers had low viral load <10^6 IU/ml, and their babies had a higher number with anti-HBs antibodies >100mIU/ml as compared with the group with high viral load (Chong *et al*., 2016). Stephen *et al.* (2014), in the USA, reported the viral load <2000IU/ml almost equal in number (44%) to the group with viral load>2000IU/ml (56%) in, a comparison between the level of anti-HBs antibodies, in the other hand, in most of the studies the high viral load associated with immune-prophylaxis failure as compared with low viral load (Sarah *et al*., 2015; Huaibin *et al*., 2011; Yun-Mi *et al*., 2007). The reason may be that most of the high viral load they have been treated with antiviral treatment might be the cause of non-response to immune prophylaxis.

The current study reported that 92.5% and 75% HBIG and hep. B vaccines were administered within the first 12 hours after birth, respectively. The babies who were recorded that they received both after 12 hours because of both hep. B vaccine and HBIG were not available at that time. In other studies, HBIG and hep. B vaccines were administered <12 hours similar to the present study (Sarah *et al*., 2015; Guo *et al*., 2017; Chong *et al*.,2016; Huaibin *et al*., 2011). In the previous two studies in the USA and China, the time of administration before and after 12 hours were associated with immune-prophylaxis failure (Sarah *et al*., 2015; Guo *et al*., 2017).

Mode of delivery has been examined as a potential risk factor for HBV transmission. In China, a study reported that 447 infants born to HBsAg positive women, 24.9% of newborns who were delivered vaginally were become infected at birth, compared with less than 10% who were delivered by cesarean section (Lee, S.D. *et al.*,1988). Another study compared outcomes of HBV infection

among three groups, infants born by spontaneous vaginal delivery, forceps or vacuum extraction, and the third group by cesarean section. The present study revealed that no significant relationship between the mode of delivery and HBV transmission. Accordingly, most obstetrical algorithms do not change in the planned mode of delivery for HBs Ag positive women regardless of HBe Ag status or level of viremia (Wang *et al*., 2002).

Decades ago, some studies demonstrated that HBs Ag could be detected in breast milk in women infected with HBV (Wong *et al.*, 1980; Lee, A.K. *et al*., 1978). More recently, several studies documented that no differences in the risk of perinatal infection transmission between breast-fed and formula-fed in vaccinated infants (De-Mortino *et al*., 1985; Hill *et al*., 2002).

The present study revealed that 60% and 63% of infants at age of 9 months and 12 months respectively were responders and their level of HBAB >10 mIU/ml. While, in other studies, the responder's percentage was higher; between 81% to 97% (Stephen *et al*., 2014; Guo *et al*., 2017; Chong *et al*., 2016; Huaibin *et al*., 2011), and that may be attributed to delay in the administration of hep. B vaccine in 37.5% of a newborn, and the vaccine storage defects.

The present study reported that the birth weight ≥2.5 kg was significantly related to high immune response; anti-HBs antibodies >10 mIU/ml (OR=1.7& CI (1.2-2.3) and no significant relation between groups of responders and non-responders at 9 and 12 months age and gender, gestational age, mode of delivery, viral load, time of administration of HBIG and hep. B vaccine and type of feeding. Different results were reported in other studies (Chong *et al*., 2016; Huaibin *et al*., 2011) where they found a significant relation between the gender, mode of delivery, feeding pattern, and low immune response did not exist. Huaibin *et al*. (2011) reported a significant relation between HBe Ag positive mothers and detectable viral load also did not associate with low immune response in infants. Stephen *et al.* (2014) in the USA reported that gestational weeks <37 weeks, time of hep. B vaccine >12 hours, and time of final dose of vaccine >6 months were associated with low response. Guo *et al*., (2017) reported that HBe Ag positive mothers and infants receiving less than one dose of HBIG were associated with low response in a study done in China.

6. Conclusion and recommendations

From the analysis, the investigators found that all infants had negative hepatitis B s Ag, so hepatitis B infection has not been chronically transmitted in the study groups. Two-thirds of the infants who responded to immune prophylaxis were at 9 months and 12 months of age, which was low as compared to other studies. The birth >2.5 kg was the only significant factor for a responder to immune prophylaxis. The investigator recommends that HBIG should be given to the positive mothers during pregnancy and to assess the titer of HBe Ag during pregnancy to know the relation between the positivity of HBe Ag and rate of transmission and need further study for influencing factors on bigger sample size.

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