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# معدل الاصابة بألتهاب الكبد الفيروسي نوع E بين الحوامل و حديثي الولادة في محافظة ديالى

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# The Rate of Hepatitis E Virus Infection among Pregnant and Neonate in Diyala Province

## A Thesis

Submitted to the Council of the College of Medicine-University of Diyala in Partial Fulfillment of the Requirements of Master's Degree of Sciences in Medical Microbiology

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# Chapter one Introduction

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# □. Introduction

## □.□. Background□

Maternal health refers to the health of women before and during pregnancy, at childbirth and during the postpartum period. It encompasses the health care dimensions of family planning, preconception, prenatal, and postnatal care in order to ensure a positive and fulfilling experience and reduce maternal morbidity and mortality (WHO, 2017), particularly among women who had poorer general maternal health (Gibson-Helm *et al*., 2015 ). Recurrent abortion is the occurrence of two or more consecutive pregnancy losses or miscarriages (it is also called spontaneous abortion or habitual abortion). It affects about 1% of pregnant women (Jeve and Davies, 2014). The causes behind recurrent pregnancy loss are variable, thus a thorough evaluation is recommended (Branch *et al*., 2010). Infections are estimated to be responsible for between 0.5 and 5% of cases with recurrent miscarriage. A wide range of pathogens; parasites, bacteria, mycoplasma, chlamydia and viruses are reported as the causative agents through the development of acute or chronic endometritis (Cicinelli *et al*., 2014; Rac *et al*., 2019).

Pregnant woman are more susceptible to certain infections caused by an increased immune tolerance in pregnancy to prevent an immune reaction against the fetus, as well as secondary maternal physiological changes including a decrease in respiratory volumes and urinary stasis due to an enlarging uterus. Therefore, pregnant women are more severely affected by certain infections, some of these are vertically transmissible (Kourtis *et al*., 2014). The importance of understanding the role of viral infection during pregnancy is becoming more relevant due to the growing risks of pandemics which may significantly affect the pregnant mother and the fetus.

Hepatitis E is inflammation of the liver caused by infection with the hepatitis E virus (HEV). Hepatitis E is one of seven known human hepatitis viruses: hepatitis A, B, C, D, E, G and transfusion transmitted virus (TTV) (Kamar *et al*., 2014). It is responsible for around 20 million infections a year with about three million acute illnesses that resulted in 44,000 deaths during 2015 (Khuroo *et al*., 2016). Hepatitis E is endemic in Central Asia and is a major cause of illness and of death in developing countries with reported outbreaks in Central America and the Middle East (Hasan *et al*., 2006; CDC, 2013). High Seroprevalence of HEV infection was documented in Eastern Mediterranean and Middle Eastern countries (Karbalaie *et al*., 2017).

The Global Burden of Disease Regions (exclusively developing countries) estimated that in 2005, there were 3.4 million symptomatic cases of HEV infections, with 70,000 deaths and 3,000 stillbirths with a significant proportion of deaths in pregnant women (Rein *et al*., 2012). Another study suggested that there may be approximately 1,000 maternal deaths per annum in Bangladesh alone (Labrique *et al*., 2012). Numerous studies from developing countries have shown excess mortality in pregnant women who develop HEV infection. Liver failure with mortality rates of 20% to 25% usually in the third trimester has been reported from outbreaks of genotype 1 and 2 HEV in developing countries. (Patra *et al*., 2007; Khuroo *et al*., 2016). Besides signs of an acute infections, adverse effects on the mother and fetus may include preterm delivery, abortion, stillbirth, and neonatal death (Khuroo. and Kamili, 2003; Tosone *et al*., 2018). Pregnant women die of obstetric problems, including hemorrhage or eclampsia, or develop fulminant hepatic failure. Stillbirths are common, as is vertical transmission to infants who survive, who have an increased neonatal morbidity and mortality with excess mortality with HEV genotypes 1 and 2 (Khuroo *et al*., 1995; Anty *et al*., 2012; Gouilly *et al*.,2018).

The cause of excess maternal mortality with HEV infection is controversial. However, it has been documented that high viral load of HEV

during pregnancy and HEV genotype could be responsible for the severity of infection during pregnancy (Kar *et al*., 2008; Borkakoti *et al*., 2013). Furthermore, Pregnancy is characterized by a state of maternal immune tolerance toward the fetus. T-cell activity is reduced, plus reduction in cytokine production in the first 20 weeks, Th2 responses predominate, and immunological changes in the placenta down regulate antigen presentation. The changes in maternal immunological responses are driven, at least in part, by significant changes in hormone profiles, with increased levels of progesterone, estrogen, and human chorionic gonadotropin (Navaneethan *et al*., 2008). Studies have shown significant differences in immunological and hormonal responses in pregnant women with fulminant hepatic failure caused by hepatitis E (Bose *et al*., 2011; Salam *et al*., 2013).

In Iraq, very limited studies were conducted exploring the prevalence of HEV infection among healthy population as well as some risky groups; these studies were performed in Diyala, Baghdad and Al-Muthanna provinces (Hasan *et al*., 2008; Utba, 2013; Muslim *et al*., 2015). For the best of our knowledge, no previous study had investigated the HEV infection among Iraqi pregnant women.

### □.□ Aims of the study□

The present study was arranged to achieve the following goals:

1. Figuring out the rate of HEV infection among pregnant women and its associated risk factors.
2. Exploring the association of HEV infection and pregnancy loss and its contributing circumstances.
3. Figuring out the rate of HEV infection among neonates with jaundice.

# Summary

Hepatitis E virus (HEV), is a small non-enveloped, icosahedral virus of about 30 nm which belongs to the new Hepevirus type classified in *Hepeviridae* family. It has a positive sense, single-stranded RNA that contains three open reading frames. HEV, is a major cause of enterically transmitted hepatitis infection which is the major causes of acute viral hepatitis in developing countries. Based on WHO data, around 20 million new cases of HEV infections take place every year worldwide. HEV is classically transmitted feco-orally, vertical transmission plus infrequent transmission by blood or blood products are reported. Globally, HEV had four major genotypes that differ in their geographical distribution and source of infection. HEV infection in pregnant women draw utmost attention, since it causes a high maternal mortality (20%-30%) that is especially severe during second and third trimesters of pregnancy in tropical countries most probably due to acute fulminant hepatic failure. HEV infection in pregnancy was linked to spontaneous abortion, stillbirth and neonatal death in 56% of newborns. The hormonal, immunological alterations plus the HEV genotype are of major contribute in HEV-related bad consequences of pregnancy. The HEV replication in placental cells could explain the high fetal and maternal mortality rates.

The aims of this study are the serological detection of IgG anti-HEV and IgM in pregnant women plus newly born with neonatal jaundice plus the exploration of the impact of certain socio-demographic and risk factors on maternal-fetal outcomes.

Three hundred and ten participants were enrolled in this cross sectional study. They were grouped into the following categories; 60 healthy pregnant women with ages ranging (17-42) years. 70 pregnant women with jaundice with age range (17- 40) years. 90 pregnant women with abortion with age range (17-40) years, and 90 neonates were included (52 males and 38 females); their ages

ranged between (2-17) days. Participants were allocated from Al-Batool Teaching Hospital for Maternity and Children and Primary Healthcare Centers in Diyala.A special questionnaire form was particularly preconstructed to this study.

The results found that the anti-HEV IgG positivity rate in pregnant women with abortion was (5.6%), in pregnant women with jaundice it was (7.1%), among the neonates with jaundice it was (4.4%), and among healthy pregnant women it was (6.7%) with a statistically insignificant difference (P = 0.891). Regarding the anti-HEV IgM positivity rate among pregnant women with abortion there was (2.2%), in pregnant women with jaundice was (4.3%), among neonate with jaundice it was (1.1%) while among healthy pregnant women was (3.3%), with a statistically insignificant difference (P = 0.623).

The Mean ± SD of anti-HEV IgG titer of pregnant women with abortion, pregnant women with Jaundice, Neonates with jaundice and healthy pregnant women were 350.4 ±724.2 IU/l, 228.1 ± 244.6 IU/l, 214.6 ±172.6 IU/l and 295.2 ± 522.9IU/l with insignificantly higher in pregnant women with jaundice (P= 0.217). Whereas, the Mean ± SD of anti-HEV IgM titer of pregnant women with abortion, pregnant women with Jaundice, Neonates with jaundice and healthy pregnant women were 118.3 ± 31.8 IU/L, 109.8 ± 38.6 IU/l, 90.7 ±11.3 IU/l and 155.3 ± 39.0 IU/l with significantly higher in healthy pregnant women compared to other study groups (P=0.0001).

In pregnant women with jaundice, the anti-HEV IgG titer was highly significant among those in the second trimster of pregnancy (P= 0.0001), and insignificantly higher among the women with abortions (P= 0.054).

The results showed that there was significantly higher titer of anti-HEV IgG among anti-HEV IgM positive women with abortions compared to those who were anti-HEV IgM negative (P= 0.037). Furthermore, the anti-HEV IgG titer was significantly higher among neonates who were anti-HEV IgM positive compared to their counterparts (P= 0.0001). Nevertheless, other variables

including women's age, previous abortion, residence and type of water consumption had insignificant associations with anti-HEV IgG.

In neonates with jaundice, although the age group 1-6 days had higher anti-HEV IgG titers; however the difference not reach the level of statistic significance (P= 0.083). Other variables; gender and type of feeding had no significant associations with anti-HEV IgG (P= 0.336 and 0.506) respectively, similarly, none of these variables were significantly associated with anti-HEV IgM titer.

Concerning the anti-HEV IgM titer, the results found that there was significantly higher anti-HEV IgM titer among pregnant women with jaundice in the second trimester of gestation compared to other women (P= 0.0001). Moreover, in pregnant women with abortions, those with 3 previous abortions had significantly higher anti-HEV IgM titer compared to others (P= 0.047). Additionally, the results found that the anti-HEV IgM titer in pregnant women with jaundice was highly significant in those women who were anti-HEV IgG positive compared to IgG negative women (P= 0.002). Similarly, among neonates with jaundice, the anti-HEV IgM titer was found to be higher among neonates with positive anti-HEV IgG compared to those IgG negative (P= 0.002). However, other variables; age, residence, type of feeding were insignificantly associated with anti-HEV IgM titer.

The correlation analyses found that in pregnant women with jaundice there was a highly significant correlation between the anti-HEV IgG titer and the duration of pregnancy (correlation coefficient r= -0.353, P= 0.003). Additionally, there was a highly significant correlation with the titer of anti-HEV IgM (r= 0.316, P= 0.008). The results also found that there highly significant correlation between IgM anti-HEV titer and IgG anti-HEV titer in gravid women with jaundice (r= 0.378, P= 0.008). On the other hand, there was a highly significant correlation among the IgM anti HEV titer and the IgG anti -HEV titer in neonates with jaundice (r= 0.378, P= 0.0001).

Accordingly, the percent study concluded that all pregnant women at least those in the second and third trimester of gestation are particularly prone for HEV infection with probable maternal-fetal serious consequences, suggesting that such women are preferably tested for HEV infection during that period.