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Review
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Hepatitis B virus infection, infertility, and assisted reproduction

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Abstract: Background: Hepatitis B virus (HBV) is one of the most widespread viruses worldwide and a major cause of hepatitis, cirrhosis, and hepatocellular carcinoma. Previous studies have revealed the impacts of HBV infection on fertility. An increasing number of infertile couples with chronic hepatitis B (CHB) virus infection choose assisted reproductive technology (ART) to meet their fertility needs. Despite the high prevalence of HBV, the effects of HBV infection on assisted reproduction treatment remain limited and contradictory. Objective: The aim of this study was to provide a comprehensive overview of the effect of HBV infection on fertility and discuss its effects on pregnancy outcomes, vertical transmission, pregnancy complications, and viral activity during ART treatment. Methods: We conducted a literature search in PubMed for studies on HBV infection and ART published from 1996 to 2022. Results: HBV infection negatively affected fertility in both males and females. Existing research shows that HBV infection may increase the risk of pregnancy complications in couples undergoing assisted reproduction treatment. The impact of HBV infection on the pregnancy outcomes of ART is still controversial. Current evidence does not support that ART increases the risk of vertical transmission of HBV, while relevant studies are limited. With the development of ART, the risk of HBV reactivation (HBVr) is increasing, especially due to the wide application of immunosuppressive therapy. Conclusions: Regular HBV infection screening and HBVr risk stratification and management are essential to prevent HBVr during ART. The determination of optimal strategy and timing of prophylactic anti-HBV therapy during ART still needs further investigation.

Key words: Assisted reproductive technology (ART); Hepatitis B virus (HBV); Immunosuppressive agent; Pregnancy

1 Introduction

Hepatitis B virus (HBV), as a member of the Hepadnaviridae family, is responsible for infecting more than 250 million people around the world, especially in the Western Pacific and African regions (Yuen et al., 2018). HBV infection is a substantial public health burden and the leading cause of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). The virus has also been detected in several extrahepatic organs, including the ovaries, testes, and kidneys (Huang et al., 2003; Ye et al., 2006). The impact of HBV infection on human reproduction has been extensively studied. HBV infection has been reported to have adverse effects on many processes involved in natural conception, including sperm quality (Lorusso et al., 2010), ovarian (Keay et al., 1998; Wang et al., 2019) and tubal function (Lao et al., 2017), and fertilization (Shi et al., 2014), aggravating the risk of infertility.

A growing number of couples with infertility issues who have chronic hepatitis B (CHB) virus infection are turning to assisted reproductive technology (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), to satisfy their reproductive demands. The problems and challenges faced by infertile couples with CHB virus infection during ART have raised many concerns. In recent years, the application of immunosuppressive therapy seems to have been gaining popularity in assisted reproduction. Previous experience in treatment with immunosuppressive

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agents mainly comes from cancer and autoimmune diseases. The application of immunosuppressive agents in the field of assisted reproduction is still in its infancy, and there is insufficient knowledge of their use in HBV-infected patients. Although the impact of HBV infection on fertility treatment has been reviewed previously (Mak and Lao, 2020), few studies have focused on the effect of ART on the viral activity of HBV.

This review begins by describing the effect of HBV infection on fertility, and then discusses its links to pregnancy outcomes, vertical transmission, pregnancy complications, and viral activity during ART treatment, with the aim to improve the management of pregnant patients with HBV infection following assisted reproduction.

2 Methods

Articles from PubMed were selected using the following keywords: assisted reproductive technology, infertility, pregnancy outcomes, vertical transmission, pregnancy complications, immunosuppression, viral activity, and hepatitis B virus. A total of 508 studies were identified via this method. After excluding duplicate studies and screening the titles and abstracts, 135 studies were found as potentially eligible. A total of 108 studies were finally included after the exclusion of no correlation studies, studies of hepatitis B complicated with other types of liver diseases, full papers that could not be retrieved, and papers published prior to 1996. The flowchart for the search methodology is presented in Fig. 1.

3 HBV infection and fertility

HBV is present in different development stages of oocytes and spermatozoa (Huang JM et al., 2003; Huang TH et al., 2005; Ye et al., 2006) and may exert negative effects on the fertility of both males and females (Table 1). A large population-based cohort study demonstrated a significantly increased incidence of infertility among men with HBV infection (Su et al., 2014). A sperm study showed that HBV-seropositive males had significantly impaired sperm quality, and the sperm concentration, sperm viability and normal morphology were all significantly reduced in males with HBV infection compared with healthy controls (Lorusso et al., 2010). Oger et al. (2011) found that HBV had a deleterious effect on sperm motility in vivo. Zheng et al. (2016) reported that active HBV infection may adversely affect the reproductive performance of testicular or epididymal aspirated sperm during ICSI. Through logistic regression analysis, Zhou et al. (2011) suggested that HBV infection could independently increase the asthenozoospermia and oligozoospermia/azoospermia rates. It has been

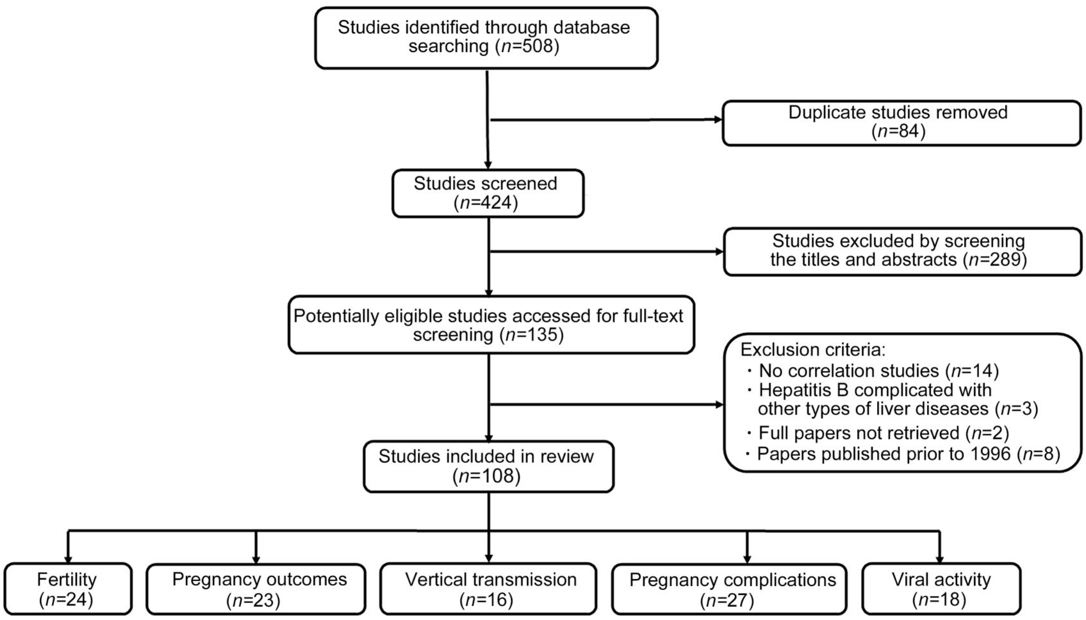

Fig. 1 Flow chart for the search methodology.

Table 1 Characteristics of included studies concerning the effect of HBV on fertility

Study	Country	Sample size (HBV^+/HBV^-)	Outcome
Ye et al. (2006)	China	30/NA	Infected and replicated in the ovum
Huang et al. (2003)	China	9/5	Mutagenic effect on sperm staining
Su et al. (2014)	China	5138/25 690	Increased risk of male infertility
Lorusso et al. (2010)	Italy	30/130	Impaired sperm quality, and significantly reduced sperm concentration, viability, and normal morphology
Oger et al. (2011)	France	32/64	Decreased sperm motility and lower fertilization rate
Zheng et al. (2016)	China	224/121	Lower fertilization during ICSI
Zhou et al. (2011)	China	457/459	Decreased sperm quality
Zhou et al. (2009)	China	NA	Decreased sperm motility
Vicari et al. (2006)	Italy	34/69	Decreased normal sperm morphology
Moretti et al. (2008)	Italy	13/20	Increased sperm apoptosis and necrosis
Kang et al. (2012)	China	NA	Increased sperm apoptosis and loss of membrane integrity
Han et al. (2021)	China	NA	Decreased sperm fertilizing capacity
Qian et al. (2016)	China	30/60	Induced IL-17 and IL-18 expression
Bei et al. (2017)	China	202/2922	Increased immune infertility
Shi et al. (2014)	China	224/448	Decreased top-quality embryo rate and fertilization rate
Ye et al. (2005)	China	18/NA	HBsAg and HBcAg expressed in the ova and ovaries
Wang et al. (2019)	China	894/7656	Increased infertility duration and ovulatory disorders
Bertoletti and Gehring (2006)	UK	NA	Increased immune response damage
Li et al. (2019)	China	37/190	Altered peripheral immune responses
Lao et al. (2017)	China	113/718	Increased tubal damage and infertility

HBV: hepatitis B virus; NA: not available; ICSI: intracytoplasmic sperm injection; IL: interleukin; HBsAg: hepatitis B surface antigen; HBcAg: hepatitis B core antigen.

acknowledged that appropriate sperm progressive motility is a key factor in male reproduction. The decrease in sperm motility in HBV-infected men, especially progressive motility, has also been confirmed by many studies (Vicari et al., 2006; Zhou et al., 2009; Oger et al., 2011). Zhou et al. (2009) found that the HBV S protein (HBs) decreased sperm motility in a dose- and time-dependent manner and that the asialoglycoprotein receptor could exert its effect on the intake of HBs into sperm cells. In addition, sperm morphology has been reported to be negatively correlated with HBV DNA load (Vicari et al., 2006). A small sample study using transmission electron microscopy analysis observed increased apoptosis and necrosis in HBV-infected patients (Moretti et al., 2008). HBs exposure has been indicated to induce increased sperm cell apoptosis and the loss of sperm membrane integrity through reactive oxygen species generation, lipid peroxidation, total antioxidant capacity reduction, phosphatidylserine externalization, caspase activation, and DNA fragmentation, eventually leading to sperm dysfunction (Kang et al., 2012). The same research team recently found that HBs could activate the B-cell lymphoma 2 (Bcl2)/Bcl2-associated X protein (Bax) signaling cascade, which triggers apoptosis-inducing factor (AIF)/endonuclease G (Endo G)-mediated apoptosis, inducing sperm DNA fragmentation, sperm damage and death, and reducing sperm fertilization ability (Han et al., 2021). Qian et al. (2016) found that HBV infection could increase malondialdehyde concentrations in semen, induce abnormal interleukin (IL)-17 and IL-18 expression, and subsequently affect reproductive capacity in infertile male patients. HBV infection has also been found to increase the incidence of male immune infertility (Bei et al., 2017), which may be related to the abnormal regulation of the blood-testis barrier (Bei et al., 2017).

In addition to poor sperm parameters, HBV may also lead to a higher risk of a lower fertilization rate (Lee et al., 2010; Oger et al., 2011; Zhou et al., 2011; Shi et al., 2014). A lower rate of top-quality embryos was found in couples with female partners who were HBV-seropositive (Shi et al., 2014). Thus, it is speculated that HBV infection may impair the quality of oocytes. Although previous studies have demonstrated the presence of hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) in the ova and granular, interstitial and endothelial cells of the ovaries (Ye et al., 2005, 2006), few studies have addressed the correlation between HBV infection and oocyte quality. HBV seropositivity was also found to be positively associated with a prolonged duration of infertility and ovulatory disorder (Wang et al., 2019). Microorganism infection can lead to a decreased ovarian response to gonadotropin stimulation (Keay et al., 1998). Furthermore, viral infection may impair fertility by causing inflammatory and immune changes or direct toxic effects (Keck et al., 1998). CHB virus infection is notably associated with immune response damage and may be a surrogate for other infections, causing changes in the microbiome in the female genital tract, thus leading to infertility (Bertoletti and Gehring, 2006). CHB virus infection can also affect the proportion and function of peripheral immune cells, including B cells, $CD3^+$ $CD4^+$ helper T cells, and natural killer (NK) cells, causing female reproductive failure (Li et al., 2019). Moreover, HBV infection may increase the risk of pelvic infection in women through an impaired immune response to sexually transmitted infections, resulting in tubal damage and infertility (Lao et al., 2017). These results show that HBV infection can lead to infertility in both males and females by affecting sperm, ovarian and tubal function, fertilization processes, and the immune system.

4 HBV infection and pregnancy outcomes of couples undergoing ART

A large retrospective study found no significant differences in the ongoing pregnancy rate or live birth rate (LBR) between HBsAg-positive and HBsAg-negative couples (Lee et al., 2010). Consistent with this finding, Shi et al. (2014) showed no significant difference in the clinical pregnancy rate (CPR) between the HBsAg-seronegative and HBsAg-seropositive groups. HBV-infected men were consistently reported to have similar CPRs after assisted reproduction compared to seronegative men (Zhao et al., 2007; Oger et al., 2011; Bu et al., 2014; Cito et al., 2021; Wang et al., 2021). A prior retrospective case control study showed that HBV infection was not an independent contributor to pregnancy outcomes after IVF treatment (Wang et al., 2019), which was further confirmed by a recent meta-analysis study (Farsimadan et al., 2021). This may be explained by the low prevalence of HBV-DNA-positive embryos in HBsAg-seropositive male couples (Hu et al., 2011) who still have access to uninfected embryos for fertilization and implantation. Notably, similar IVF outcomes were found by a previous study in HBV-infected men compared with control individuals; however, HBV infection in men was associated with significantly lower rates of two-pronuclear fertilization, implantation, and clinical pregnancy in couples undergoing ICSI cycles (Zhou et al., 2011). The decreased CPR during the ICSI cycle may be related to the reduction in high-grade embryo acquisition (Zhou et al., 2011). In addition, ICSI may lead to the introduction of extracellular HBV into oocytes (Lutgens et al., 2009). ICSI together with sperm-washing techniques may provide a promising way to improve pregnancy outcomes (Jindal et al., 2016; Cito et al., 2019). During frozen-thawed embryo transfer (FET) cycles, paternal HBV infection has shown a negative association with the CPR, probably resulting from the adverse effects of HBV on the ability of embryos to survive the freezing process and their development potential after thawing (He et al., 2018). It has been speculated that sperm-introduced HBV may affect the expression of genes related to environmental stress tolerance in embryos (He et al., 2018).

Nevertheless, a small retrospective cohort study demonstrated that couples with discordant HBV status had significantly decreased pregnancy rates compared with age-matched controls (Pirwany et al., 2004). However, there was no distinction between male or female partners who were seropositive for HBV. Studies concerning the impact of female HBV infection on pregnancy outcomes have reached different conclusions. Cantalloube et al. (2021) reported negative effects of HBV infection in women on cumulative LBR after IVF. On the other hand, Chen et al. (2014) and Bourdon et al. (2021) suggested that HBV infection in women was not associated with the outcomes of IVF/ICSI treatments. Surprisingly, Lam et al. (2010) demonstrated that pregnancy and implantation rates were significantly higher among couples with women who were seropositive for HBV but not among those with affected husbands. The explanation for this phenomenon might be that IVF and embryo transfer (ET) therapy can overcome some inhibitive effects on sperm caused by inflammatory changes in the lower genital tract in women infected with HBV. All semen samples were processed through standardized procedures to eliminate the cause of lower pregnancy rates. In line with this finding, women with HBV DNA detectable in the follicular fluid showed a trend toward a higher ongoing pregnancy rate/LBR per cycle (Mak et al., 2019). However, gestational age at delivery was found to be lower in the female hepatitis B e antigen (HBeAg) group after IVF-ET, which may be correlated with liver damage caused by CHB virus infection (Lin et al., 2015). A previous systematic review and meta-analysis provided some insights into the effects of four patterns of biparental HBV infection on pregnancy outcomes after ART treatment, including paternal and maternal coinfection, either maternal or paternal infection, maternal HBV infection alone, and paternal HBV infection alone (Xiong et al., 2022). They found that maternal HBV infection was not associated with a lower CPR and LBR at the per-woman level, whereas paternal HBV infection alone could reduce the CPR at the per-cycle level (Xiong et al., 2022). In summary, the impact of HBV infection on the pregnancy outcomes of ART is still controversial, prompting further research (Table 2).

5 Risk of vertical transmission of HBV during ART

The risk of mother-to-child transmission (MTCT) in women with CHB virus infection is related to viral load. MTCT is more likely to occur in mothers who are HBeAg-positive or have high HBV DNA levels (Steyaert et al., 2000; Wen et al., 2013). According to the European Association for the Study of the Liver (EASL) guidelines, mothers with serum HBV DNA levels >10^6 IU/mL carry a >10% risk of MTCT (European Association for the Study of the Liver, 2012). Thus, antiviral therapy is needed to reduce this risk. The vertical transmission of HBV can occur at any stage of pregnancy, including the intrauterine, perinatal and postpartum periods, and even through infected germ cells (Liu et al., 2021). HBV messenger

Table 2 Characteristics of included studies concerning the effect of HBV on pregnancy outcomes of ART

Study	Country	Sample size (HBV^+/HBV^-)	Outcome
Lee et al. (2010)	China	131/1545	No effect on ART outcomes
Shi et al. (2014)	China	224/448	No effect on pregnancy rates
Oger et al. (2011)	France	32/64	No effect on pregnancy rates
Cito et al. (2021)	Italy	66/68	No effect on pregnancy rates
Wang et al. (2021)	China	227/454	No effect on ART outcomes
Zhao et al. (2007)	China	102/204	No effect on IVF-ET outcomes
Wang et al. (2019)	China	894/7656	No effect on pregnancy rates
Hu et al. (2011)	China	NA	HBV DNA was present in 9.6% of oocytes and 14.4% of embryos
Zhou et al. (2011)	China	457/459	No effect on IVF outcomes
Pirwany et al. (2004)	Canada	13/27	Decreased implantation and pregnancy rates
He et al. (2018)	China	37/78	Decreased clinical pregnancy rate after FET
Lam et al. (2010)	China	56/231	Increased pregnancy and implantation rates of IVF
Xiong et al. (2022)	China	NA	No effect on pregnancy rates of ART
Farsimadan et al. (2021)	Iran	NA	No effect on pregnancy outcomes of IVF
Lin et al. (2015)	China	305/199	Decreased delivery gestational age of IVF-ET
Chen et al. (2014)	China	123/246	No effect on IVF/ICSI outcomes
Mak et al. (2019)	China	28/36	Increased ongoing pregnancy/live birth rate per cycle of IVF/ICSI
Jindal et al. (2016)	USA	NA	ICSI and sperm washing technology could reduce the virus transmission risk of ART
Bu et al. (2014)	China	20/257	Male HBV infection has no effect on pregnancy rates
Cantalloube et al. (2021)	France	64/128	Decreased cumulative live birth rates after IVF
Bourdon et al. (2021)	France	114/121	No effect on cumulative live birth rates after IVF/ICSI

HBV: hepatitis B virus; ART: assisted reproductive technology; NA: not available; IVF: in vitro fertilization; ET: embryo transfer; FET: frozen-thawed embryo transfer; ICSI: intracytoplasmic sperm injection.

RNA (mRNA) was detected in the embryos of HBV-infected women following IVF, confirming the vertical transmission of HBV through the ovum (Ye et al., 2013). HBV DNA fragments are able to enter oocytes through the zona and oolemma and then integrate into their chromosomes, and subsequently persist in the embryo as fertilization proceeds (Huang et al., 2005). Maternal HBV DNA levels and HBeAg status were found to impact HBV expression and replication in the ovum (Kong et al., 2016). Sperm has also been shown to be a vector for the vertical transmission of HBV DNA to the next generation, which can be introduced into oocytes by integration into the human sperm genome (Ali et al., 2005). A Japanese study using homology analysis and phylogenetic analysis found high nucleotide homology (99.3%–100.0%) between five sets of fathers and their children, which provides important evidence for the fact that father-to-child transmission is an important route of HBV infection (Tajiri et al., 2007). Vertical transmission from fathers to fetuses has also been proven by direct sequencing (Wang et al., 2003). The integration of HBV DNA into sperm chromosomes occurs in multiple sites and is nonspecific, which can increase the instability of sperm chromosomes (Huang et al., 2003). HBV infection can exert its genetic effects by altering genetic constituents and/or inducing chromosome aberrations (Huang et al., 2003). Sperm-mediated HBV genes can replicate and be expressed in early embryos (Ali et al., 2006; Kong et al., 2017). It has been reported that host genes may be involved in the regulation of sperm-introduced HBV gene transcription in embryos (Zhong Y et al., 2017). HBV cytosine-phosphate-guanine (CpG) sites can be methylated in HBV-infected patient sperm cells before maturation (Zhong CY et al., 2017). In both sperm and sperm-derived embryos, CpG site methylation in islands II and III is involved in the transcriptional regulation of the HBV *X* and *S* genes, respectively (Zhong CY et al., 2017). The HBV X protein is necessary for the initiation and maintenance of HBV replication (Lucifora et al., 2011).

A former prospective cohort study suggested that assisted conception was not associated with an increased risk for the MTCT of HBV infection compared with spontaneous pregnancy (Nie et al., 2019). Although this study found that children conceived by ICSI who were born to HBsAg-positive mothers had higher rates of HBsAg positivity than children conceived by IVF, the difference failed to reach statistical significance (Nie et al., 2019). The impact of ICSI on MTCT is not yet conclusive. In accordance with this finding, Yi et al. (2022) established that IVF-ET had no detrimental effects on MTCT in women with chronic HBV infection based on prophylactic immunization. It is speculated that the effect of HBV on embryonic development and implantation may be responsible for the undetected increased risk (Nie et al., 2019; Yi et al., 2022). A long-term follow-up study also implied that the presence of HBsAg in oocytes and embryos may not lead to the vertical transmission of HBV to offspring of HBV carriers (Jin et al., 2016). However, the HBV markers of children were obtained after full vaccination, and postnatal vaccines were still effective against small amounts of HBV in embryos (Jin et al., 2016). The above studies suggest that ART may not increase the risk of MTCT of HBV (Table 3). Meanwhile, few studies have assessed the risk of father-to-child HBV transmission during ART.

6 HBV infection and the risk of pregnancy complications

The impacts of HBV infection on pregnancy complications are of growing concern (Table 4), particularly the relationship between HBV infection and gestational diabetes mellitus (GDM). A retrospective cohort analysis of 85 190 women revealed no significant difference between a group of women with CHB virus infection and the control group concerning the prevalence of GDM (Zhang et al., 2020). A population-based study reached the same conclusion that HBV infection did not seem to increase the risk of GDM in women undergoing ART (Xiong et al., 2021). However, many studies have confirmed that HBsAg positivity is an independent risk factor for GDM (Peng et al., 2019; Yin et al., 2021, 2023; Zhao et al., 2022). Abnormal liver function was found to be an independent risk factor for GDM in HBV-infected women (Zhou et al., 2022). Two meta-analyses further confirmed the positive correlation between HBV infection and GDM (Tan et al., 2018; Farsimadan et al., 2021). Ethnic differences and different diagnostic criteria may account for the inconsistent results (Yue et al., 1996; Tan et al., 2018). Another study reported that different viral activity among the included subjects

Table 3 Characteristics of included studies concerning the risk of vertical transmission of HBV during ART

Study	Country	Sample size (HBV^+/HBV^-)	Outcome
Wen et al. (2013)	China	303/NA	High viral load increased risk of MTCT
Ye et al. (2013)	China	38/NA	HBV mRNA was detected in embryos
Huang et al. (2005)	China	NA	HBV DNA was detected in oocytes
Kong et al. (2016)	China	50/6	Viral load affected HBV expression and replication in the ovum
Ali et al. (2005)	China	NA	Vertical transmission through sperm
Tajiri et al. (2007)	Japan	13/NA	Vertical transmission from father to fetus
Wang et al. (2003)	China	8/NA	Vertical transmission from father to fetus
Kong et al. (2017)	China	18/50	HBV mRNA was detected in IVF embryos of HBV-infected fathers
Ali et al. (2006)	China	NA	Sperm-mediated HBV genes can replicate and express in early embryonic cells
Zhong Y et al. (2017)	China	NA	Host genes regulated transcription of sperm-introduced HBV genes in embryo
Zhong CY et al. (2017)	China	11/11	HBV CpG site methylation involved in transcriptional regulation of HBV genes
Lucifora et al. (2011)	Germany	NA	HBx was necessary to initiate and maintain HBV replication
Nie et al. (2019)	China	23/282	ART did not affect the risk of MTCT
Yi et al. (2022)	China	224/74	IVF-ET did not affect the risk of MTCT of HBV-infected mothers
Jin et al. (2016)	China	31/41	IVF-ET did not affect the risk of MTCT

HBV: hepatitis B virus; ART: assisted reproductive technology; NA: not available; MTCT: mother-to-child transmission; mRNA: messenger RNA; IVF: in vitro fertilization; CpG: cytosine-phosphate-guanine; HBx: hepatitis B X protein; ET: embryo transfer.

Table 4 Characteristics of included studies concerning the effect of HBV on the risk of pregnancy complications

Study	Country	Sample size (HBV^+/HBV^-)	Outcome
Zhang et al. (2020)	China	9699/73 076	No effect on GDM
Xiong et al. (2021)	China	795/6216	Increased ICP risk, but no effect on other pregnancy complications or neonatal outcomes for pregnant women who underwent ART
Yin et al. (2021)	China	3039/36 500	Increased risks of GDM, ICP, and pre-eclampsia
Zhao et al. (2022)	China	10 355/89 686	Increased GDM risk
Peng et al. (2019)	China	964/964	Increased GDM risk
Zhou et al. (2022)	China	1390/NA	Age and abnormal liver function increased GDM risk
Cheung et al. (2022)	China	158/521	No effect on pregnancy complications
Sirilert et al. (2014)	Thailand	1446/21 812	Increased risk of preterm birth, low birth weight, and GDM
Wu (2019)	China	196/NA	Viral load affected the glucose level
Wang et al. (2018)	China	480/530	CDKN2A rs10811661 and rs564398 polymorphisms increased GDM risk
Tse et al. (2005)	China	253/253	Increased risk of GDM, antepartum haemorrhage, and threatened preterm labor
Reddick et al. (2011)	USA	814/296 218	Increased preterm birth risk
Stokkeland et al. (2017)	Sweden	2990/109 079	Increased preterm birth risk
Liu et al. (2017)	China	20 827/489 965	Increased preterm birth risk
Zheng et al. (2021)	China	1302/12 813	Viral load was not associated with preterm birth rate
Elefsiniotis et al. (2011a)	Greece	102/NA	Viral load was associated with preterm birth rate
Xu et al. (2021)	China	2151/52 094	Increased preterm birth risk
Wu et al. (2020)	China	1146/18 345	Increased risks of GDM, ICP, preterm birth, and neonatal asphyxia
Cai et al. (2019)	China	346/2983	Increased risks of ICP and premature rupture of membranes
Safir et al. (2010)	Israel	NA	Increased risks of preterm deliveries, premature rupture of membranes, and placental abruption
Huang et al. (2014)	Canada	NA	No effect on placental abruption or placenta previa
Tan et al. (2018)	China	NA	Increased GDM risk
Ma et al. (2018)	China	NA	Increased preterm birth risk
Jiang et al. (2020)	China	NA	Increased risk of ICP
Huang et al. (2016)	Canada	NA	Decreased risk of preeclampsia

HBV: hepatitis B virus; NA: not available; GDM: gestational diabetes mellitus; ART: assisted reproductive technology; ICP: intrahepatic cholestasis of pregnancy.

may also contribute to the conflicting evidence and that HBeAg positivity or higher levels of HBV DNA during pregnancy were not associated with pregnancy complications (Cheung et al., 2022). Nevertheless, research regarding the correlation between an increased risk of GDM and HBeAg status and viral load in women with CHB virus infection has shown paradoxical findings (Sirilert et al., 2014; Peng et al., 2019; Wu, 2019; Yin et al., 2021). Liver damage caused by HBV infection may result in impaired glucose metabolism, which may be a potential cause of GDM. Wang et al. (2018) found that CDKN2A rs10811661 and rs564398 polymorphisms were associated with an increased risk of HBV-related GDM among the Chinese population. The additional systemic inflammatory response caused by CHB virus infection may be related to the pathogenesis of GDM and other obstetric complications, including antepartum hemorrhage and threatened preterm labor (Tse et al., 2005). The placental inflammatory response is a known risk factor for preterm birth (Reddick et al., 2011). Other HBV-related risk factors, such as drug use and lower socioeconomic status, also correlate with preterm labor (Reddick et al., 2011). Previous research has shown that HBV infection increases the risk of preterm birth (Liu et al., 2017; Stokkeland et al., 2017; Ma et al., 2018; Farsimadan et al., 2021; Sirilert and Tongsong, 2021), which does not appear to be affected by HBV DNA levels (Zheng et al., 2021). However, previous studies found a significant association between HBV DNA in the cord blood of HBV-infected pregnant women and spontaneous preterm birth (Elefsiniotis et al., 2011a, 2011b). Different clinical states of CHB virus infection were reported to be independently associated with a higher risk of overall preterm birth and its subtypes, including spontaneous and iatrogenic preterm birth (Xu et al., 2021). HBV positivity in pregnant women may also increase the risk of intrahepatic cholestasis in pregnancy (Jiang et al., 2020; Wu et al., 2020; Xiong et al., 2021), preeclampsia (Huang et al., 2016; Yin et al., 2021), and premature rupture of membranes (Safir et al., 2010; Cai et al., 2019). A previous meta-analysis found no significant association between CHB virus infection and the risks of placental abruption and placenta previa (Huang et al., 2014). However, due to the limited number of included studies, more original research is needed to validate this result.

7 Viral activity of HBV in ART

Few studies have focused on HBV viral activity during ART therapy. A previous prospective study aimed to explore whether ovarian stimulation could stimulate the proliferation of HBV present in ovarian follicles and found that 40% of HBV-infected women had a significant viral replication stimulation during IVF. It was suggested that these women may have specific indications for antenatal antiviral therapy (Mak et al., 2020).

It is noteworthy that the risk of HBV reactivation (HBVr) may increase with the widespread use of immunosuppressive therapy during ART (Table 5). Maternal immune tolerance plays an important role in embryo implantation (Sheikhansari et al., 2020). Immunosuppressive agents may be used in women undergoing ET for their immunomodulatory function, especially in patients with immunological factor-dependent recurrent implantation failure (RIF) (Sheikhansari et al., 2020). RIF refers to the failure to achieve pregnancy after at least three high-grade ETs (Sheikhansari et al., 2020). Nevertheless, clinical experience with immunosuppressive treatments in HBV-infected women following IVF has been limited. HBVr may occur in patients with CHB virus infection or negative seroconversion, which is most likely triggered by the use of immunosuppressive drugs (Etienne et al., 2022). Patients with mild cases may present with reversible liver cell damage and those with severe cases may even exhibit liver failure. HBVr is based on the persistence of the viral genome as covalently closed circular DNA (cccDNA) in hepatocytes and occurs when immunosuppression mediates the weakening of host immune control (Chang et al., 2022).

The general principles of current international guidelines for the prevention of HBVr include screening for HBV infection, stratification of the risk of HBVr, and risk-adjusted management strategies (Etienne et al., 2022). It is recommended that all patients scheduled to receive immunosuppressive therapy should be screened for HBV infection markers, including anti-HBC and HBsAg, followed by HBV DNA testing if the result for either method test is positive (Etienne et al., 2022). Current evidence regarding anti-HBs as part of screening remains controversial (Su and Lim, 2019). According to the American Gastroenterological Association (AGA) guidance (Reddy et al., 2015), risk

Table 5 Characteristics of included studies concerning the effect of ART on the viral activity of HBV

Study	Country	Sample size (HBV^+/HBV^-)	Outcome
Mak et al. (2020)	China	64/NA	Increased HBV replication after IVF
Etienne et al. (2022)	Switzerland	4/NA	Immunosuppressive therapy increased the risk of HBVr
Zhong et al. (2022)	China	1303/NA	Corticosteroid increased the risk of HBVr
El Jamaly et al. (2022)	Australia	NA	TNF-α inhibitor increased HBVr risk in chronic HBV patients
Xie et al. (2007)	China	NA	Cyclosporine A inhibited the HBV replication
Huang et al. (2020)	China	NA	Cyclosporine A reduced the risk of preeclampsia
Cheng et al. (2022)	China	62/84	Cyclosporine A promoted the pregnancy outcomes of ART
Funk et al. (2021)	Canada	NA	Peripartum antiviral prophylaxis did not increase the risk of infant or maternal safety outcomes
Sheikhansari et al. (2020)	Iran	NA	Immunosuppressive agents may be used in women undergoing IVF
Chang et al. (2022)	Republic of Korea	NA	Immunosuppressive therapies may cause HBVr
Reddy et al. (2015)	USA	NA	HBVr risk stratification based on immunosuppressive regimen and serological status
Perrillo et al. (2015)	USA	NA	Immunosuppressive therapy increased the risk of HBVr
Xia et al. (2005)	China	NA	Cyclosporine A inhibited the HBV replication
Onorato et al. (2021)	Italy	NA	Strategies are modulated according to the risk profile of HBVr
Lee et al. (2021)	Republic of Korea	NA	Tenofovir was safe and effective for prevention of MTCT of HBV

ART: assisted reproductive technology; HBV: hepatitis B virus; NA: not available; IVF: in vitro fertilization; HBVr: HBV reactivation; TNF-α: tumor necrosis factor-α; MTCT: mother-to-child transmission.

stratification should be conducted based on the immunosuppressive regimen and serological status. The risk of HBVr can be categorized into high (>10%), moderate (1%–10%), and low (<1%) (Perrillo et al., 2015). Among the immunosuppressive drugs involved in AGA risk classification, prednisone and tumor necrosis factor-α (TNF-α) inhibitors are both used for the immunomodulatory management of RIF (Reddy et al., 2015). Corticosteroids induce HBVr by inhibiting the function of cytotoxic T cells and directly stimulating the HBV genome sequence (Perrillo et al., 2015). The AGA guidelines ascertain that the use of moderate- to high-dose corticosteroids (i.e., ⩾10 mg of prednisone daily or equivalent for ⩾4 weeks) leads to a high risk of HBVr, and the use of low-dose corticosteroids (i.e., <10 mg of prednisone daily or equivalent for ⩾4 weeks) results in a moderate risk of HBVr when HBsAg is positive (Reddy et al., 2015). A recent prospective study suggested that using a time-weighted average prednisone dose greater than 20 mg/d would be considered to increase the risk for HBVr or hepatitis flare (Zhong et al., 2022). TNF-α inhibitors may lead to HBVr by blocking the TNF-α-mediated antiviral pathway (Chang et al., 2022). A recent meta-analysis found that the prevalence of HBVr in the chronic carrier and occult HBV groups receiving adalimumab (TNF-α inhibitor) was 17.1% and 5.0%, respectively (El Jamaly et al., 2022). However, cyclosporine A (CsA) has been shown to inhibit HBV replication (Xia et al., 2005; Xie et al., 2007), which can promote trophoblast proliferation, invasion, and migration (Huang et al., 2020) and improve pregnancy outcomes (Cheng et al., 2022), along with immunosuppressive effects (Huang et al., 2020). There is no definitive consensus on the best strategies to prevent HBVr in HBV-infected women requiring immunosuppressive agents during ART treatment. As recommended by international guidelines, prophylactic anti-HBV therapy should be performed in HBsAg-positive patients with a moderate-high risk of HBVr (Chang et al., 2022). For HBsAg-negative patients, antiviral prevention is advised in high-risk groups (Chang et al., 2022). If HBV DNA is positive at baseline in HBsAg-negative or anti-HBc-positive patients, prophylaxis therapy similar to that in patients with overt infections should be provided (Onorato et al., 2021). It is generally suggested that antiviral therapy is started before immunosuppressive therapy and continued for at least six months after the cessation of immunosuppression (Chang et al., 2022). High-resistance barrier drugs, such as tenofovir, tenofovir alafenamide, or entecavir, are recommended for antiviral prophylaxis or treatment (Stasi et al., 2021).

However, for women undergoing ET, the safety of antiviral prophylaxis during pregnancy also needs to be considered. Among the available antiviral drugs, tenofovir disoproxil fumarate has been proven to be safe and effective for the prevention of HBV MTCT (Funk et al., 2021; Lee et al., 2021). The EASL recommends liver function testing and HBV DNA monitoring every 3–6 months for patients receiving antiviral prophylaxis (European Association for the Study of the Liver, 2017).

8 Summary

Considering the high prevalence of HBV, it is meaningful to study the effects of HBV infection on fertility, especially in patients receiving ART treatment. A large number of studies have shown that HBV negatively affects fertility in both males and females. Existing data shows that HBV infection may increase the risk of pregnancy complications in couples undergoing ART. Meanwhile, the effects of HBV infection on ART pregnancy outcomes remain controversial. Currently, there is no evidence that assisted reproduction would increase the risk of vertical transmission of HBV, although relevant studies are limited. With the development of ART, the risk of HBVr increases, especially due to the wide application of immunosuppressive therapy. Regular HBV infection screening and HBVr risk stratification and management are essential to prevent HBVr during ART. The optimal strategy and timing of prophylactic anti-HBV therapy during ART still need further elucidation.

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Author contributions

Writing – original draft: Lingjian ZHANG and Fangfang ZHANG. Writing – review & editing: Jie JIN and Zhiyuan MA. Data curation, figures, and tables: Lingjian ZHANG, Fangfang ZHANG, and Zhiyuan MA. Project administration and supervision: Jie JIN. Funding acquisition: Jie JIN and Zhiyuan MA. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Lingjian ZHANG, Fangfang ZHANG, Zhiyuan MA, and Jie JIN declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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