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Positive hepatitis B surface antigen leads to a decrease in ovarian reserve in infertile patients receiving first in vitro fertilization treatment

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Abstract

Background This study assessed the impact of chronic hepatitis B virus (HBV) infection on ovarian reserve in women.

Methods We analyzed data from 38,861 infertile women undergoing their first in vitro fertilization (IVF) treatment (2016–2022), including 1574 HBsAg-positive cases. A control group of 1574 HBsAg-negative women was matched by age and body mass index (BMI). Comparison of clinical characteristics, antral follicle count (AFC), follicle-stimulating hormone (FSH), luteinizing hormone (LH)/FSH ratio, anti-Müllerian hormone (AMH), gonadotropins (Gn) days, total Gn dosage, number of retrieved oocytes, number of mature metaphase II (MII) oocytes, and the proportion of patients with diminished ovarian reserve (DOR; AMH < 1.1 ng/ml) between two groups.

Results HBsAg-positive women showed lower basal AFC and AMH, higher basal FSH, received more Gn, and had fewer retrieved and MII oocytes than HBsAg-negative women. No significant differences in ovarian reserve or stimulation outcomes were found between e antigen-positive and e antigen-negative HBV-infected groups. DOR was less prevalent in HBsAg-negative women, and logistic regression indicated a higher DOR risk with HBV infection.

Conclusions HBsAg positivity significantly impairs ovarian reserve in women, but e antigen status does not notably affect it among HBV-infected individuals.

Keywords Hepatitis B virus, Ovarian reserve, Infertility, In vitro fertilization, Female

Background

Infertility affects 186 million people worldwide [1]. Approximately 50% of infertility cases are due to female factors, while 20–30% are caused by a combination of both male and female factors [2]. Consequently, infertility has become a significant social burden for women. Ovarian reserve function refers to the number and quality of remaining oocytes, which can reflect a woman's fertility potential [3]. A decrease in ovarian reserve function means a reduction in the ovarian response compared to women of the same age. The specific reasons for diminished ovarian reserve (DOR) are not yet clear. However, factors such as age, chemotherapy, genetics, pelvic

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surgery, smoking, etc., can lead to a decrease in the number of eggs and reproductive potential [4].

Hepatitis B virus (HBV) infection is a major public health issue worldwide; roughly 30% of the world's population shows serological evidence of current or past infection [5]. China is one of the most highly endemic areas for HBV infection. Due to the high prevalence of HBV, there is growing global concern over the potential impact of HBV upon fertility. HBV can be found not only in the liver and blood but also in the saliva, vaginal secretions, semen, and other tissues such as ovarian tissue [6, 7]. In addition, hepatitis B surface antigen (HBsAg) is detected in the ovum and follicular fluid [8, 9]. The weighted prevalence of HBsAg seropositive status among fertile women of childbearing age in China ranges from 2.4 to 10.5% [10–13]. Therefore, the correlation between HBV infection and female fertility should be considered a remarkable current issue. A large number of previous studies have reported the effect of female HBsAg patients on IVF/ICSI (in vitro fertilization/intracytoplasmic sperm injection) outcomes, and some controversial conclusions have been reached [13–17]. Priwany et al. reported that HBV infection is negatively correlated with embryo implantation and pregnancy rates [18]. Most of the studies suggested that maternal chronic hepatitis B virus infection does not affect pregnancy outcomes in infertile patients receiving IVF/ICSI treatment [16, 19–21].

However, the relationship between hepatitis B and ovarian reserve function is currently not clear. Given the lack of viable data on this issue, we carried out this case–control study to investigate the effects of HBsAg seropositive women on ovarian reserve. As far as we know, no studies have reported the effect of the hepatitis B virus on ovarian reserve function in women.

Methods

Patients

This retrospective cohort study initially included 59,609 patients undergoing their first IVF treatments in two assisted reproductive centers from January 2016 to April 2022. After exclusions, 1574 HBsAg seropositive and 37,287 HBsAg seronegative women were included in the study. For comparative analysis, we created a 1:1 matched control group using SPSS 27.0 software, with all controls being negative for hepatitis B surface antigen. The matching factors included age (with a difference of less than 1 year) and body mass index (BMI) (within 1 unit difference). These criteria were met by searching through our database of patients who were negative for hepatitis B. For each case, we selected the first available patient who met all matching criteria and had the closest matching characteristics as the control. A flow chart of the inclusion process is shown in Fig. 1. This retrospective study was approved by the reproductive research of the Reproductive Medicine Ethics Committee of Sichuan Provincial People's Hospital (Approval number: 20240402).

All patients' basic information, including their age, BMI, duration of infertility, type of infertility, and causes of infertility, were collected from the patient's electronic medical record system on March 1, 2024. All patients were routinely and systematically screened for HBsAg in the serum via enzyme immunoassay.

Exclusion criteria: acute Hepatitis, acute pelvic inflammatory disease, polycystic ovarian syndrome, history of endometriosis and ovarian surgery, history of malignant tumors, chemotherapy and radiotherapy history, autoimmune diseases, positive for HCV, HIV, and syphilis.

Controlled ovarian hyperstimulation protocol

All patients received the routine protocol for ovulation induction. Human menopausal gonadotropin (HMG), recombinant follicle-stimulating hormone (FSH), or urinary FSH were used for ovarian stimulation. The starting dose of gonadotropins (Gn) was determined based on the age, BMI, antral follicle count (AFC), and anti-Müllerian hormone (AMH) of the women and their previous responses to treatment. Ovarian response was monitored through serum E2 concentrations and ultrasound from stimulation day 5 or 6 onward. When at least three mature follicles with a diameter greater than or equal to 17 mm or two follicles with a diameter greater than or equal to 18 mm were present, a single dose of human chorionic gonadotropin (HCG) ranging from 5000 to 10,000 IU or recombinant HCG 250 μg was administered, and approximately 36 h later, oocyte retrieval was performed under ultrasound-guided transvaginal aspiration.

Outcome measures

Ovarian reserve tests include both biochemical tests and AFC. Biochemical tests of ovarian reserve include measurement of AMH, luteinizing hormone (LH), and FSH on day 2 or 3 of the menstrual cycle. The AFC describes the total number of follicles measuring 2–10 mm in diameter that are observed on day 2 or 3 of the menstrual cycle trans vaginal ultrasonographic scan. The diagnostic criteria for diminished ovarian reserve (DOR) are AMH < 1.1 ng/ml. In addition, statistics on the use of ovulation-inducing drugs: duration of Gn usage, total amount of Gn used, number of retrieved eggs, and number of mature (MII) eggs.

Statistics

Using SPSS 27.0 statistical software for statistical analysis; the Kolmogorov–Smirnov test was used to test the normality of metric data; non-normal distribution data or ordinal data were represented by Median

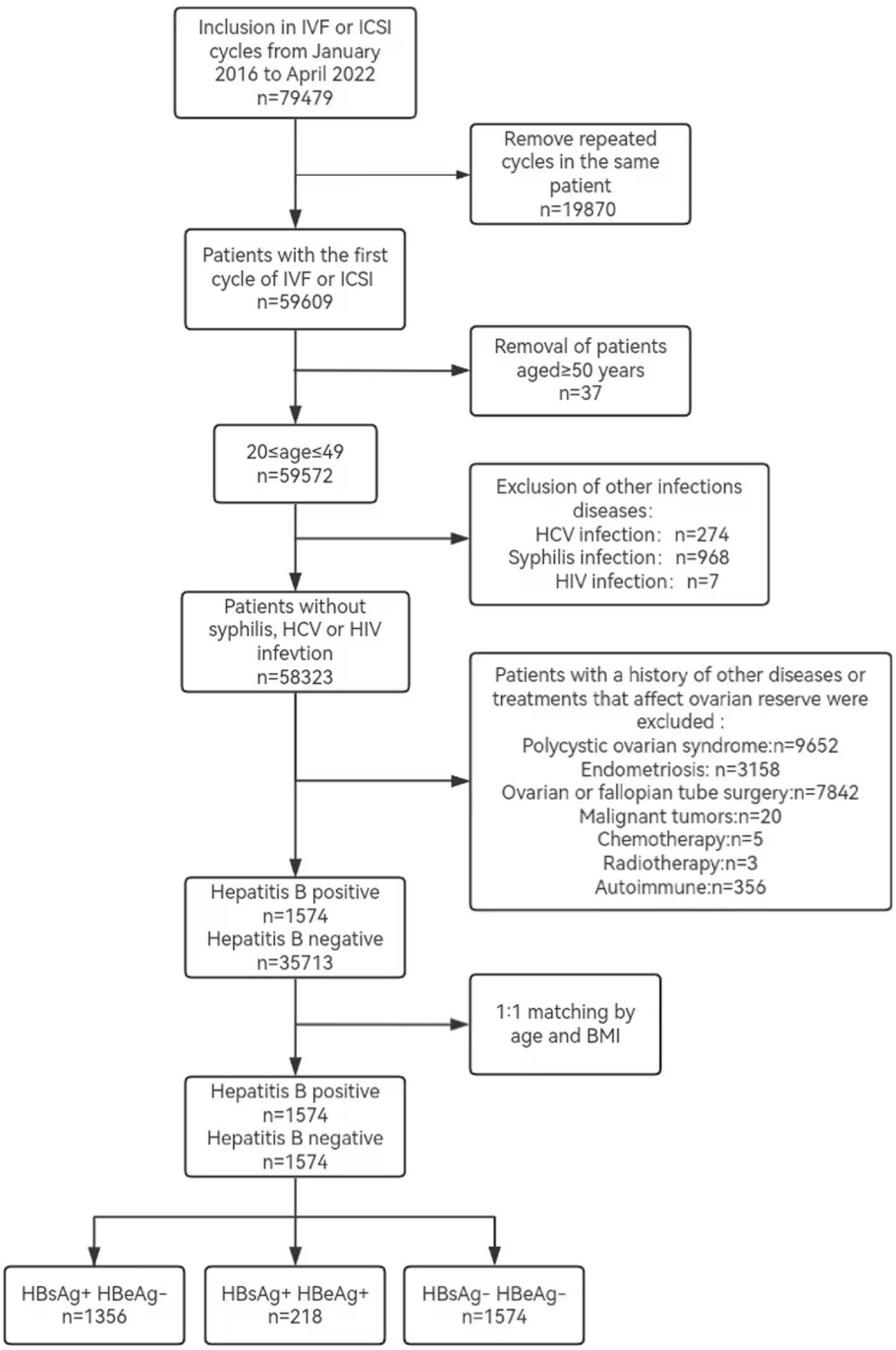

Fig. 1 The flow chart of the inclusion and exclusion process

(P25, P75), and group comparisons were analyzed using Kruskal–Wallis *H* rank sum test, and pairwise comparisons between groups were conducted using the Bonferroni method; count data was represented by frequency and percentage (*n*, %), and the comparison of rates between two groups is conducted using the chi-square test. In all comparisons, data were considered to be statistically significant with a two-tailed $P < 0.05$.

Results

In this study, we investigated 38,861 couples who underwent the first IVF-ET treatment. Among them, there were 1574 (4.0%) HBsAg-positive patients, including 1356 (3.5%) HBsAg-positive hepatitis B e antigen (HBeAg)-negative patients and 218 (0.5%) HBsAg-positive HBeAg-positive patients.

As shown in Table 1, the median age of the HBsAg-positive and HBsAg-negative groups was 32 years (IQR 30–36), and the median BMI of the HBsAg-positive and control groups was 21.45 kg/m^2 (IQR 19.65–23.73) and 21.41 kg/m^2 (IQR 19.78–23.56), respectively. Compared to the control group, the HBsAg-positive group had a longer duration of infertility (3 [2, 6] vs 3 [2, 5] years, $P<0.001$). There was no statistically significant difference in the proportion of primary and secondary infertility types between the two groups ($P=0.086$).

Association of HBV infection and ovarian reserve function

Table 2 shows the comparison of ovarian reserve function between the two groups. Compared to the control group, the HBsAg-positive group had significantly lower ovarian reserve function, characterized by higher FSH levels, fewer AFC, lower AMH levels, and LH/FSH ratio ($P<0.001$ for all). There was no statistically significant difference in the duration of Gn stimulation between the two groups ($P=0.116$), but the HBsAg-positive group required a higher total amount of Gn, while having lower numbers of retrieved and MII oocytes ($P<0.001$ for both).

Table 3 presents the results of the subgroup analysis. In the HBsAg-positive group, there were 1356 cases (86.15%) with negative e antigen and 218 cases (13.85%) with positive e antigen. Compared to the control group, both the e antigen-positive and e antigen-negative groups showed significantly lower AFC, LH/FSH ratio, AMH levels, numbers of retrieved and MII oocytes, and significantly higher FSH levels ($P<0.001$ for all). There was no statistically significant difference between the e antigen-positive and e antigen-negative groups. The duration of Gn stimulation did not differ significantly among the three groups. We found that in different age groups (20–29, 30–34, 35–39, and ≥40 years), the HBsAg-positive group showed significantly poorer ovarian reserve function and stimulation outcomes compared to the control group (Additional file 1: Table S1).

Association of HBV infection and DOR

The proportion of patients with DOR in the HBsAg-negative group is significantly lower than in the hepatitis B antigen positive e antigen-negative group and e antigen-positive group (0.38% versus 23.08% versus 19.27%), and there is no statistical difference between the latter two groups ($P=0.211$). Multivariate logistic regression analysis showed that the risk of DOR was significantly higher in the HBV-positive group (OR: 103.9, 95% CI

Table 1 The demographic data of HBsAg positive group and HBsAg negative group

	HBsAg$^+$($n=1574$)	HBsAg$^-$($n=1574$)	*P*
Age (years)	32 (30,36)	32 (30,36)	> 0.999
BMI (kg/m^2)	21.45 (19.65,23.73)	21.41 (19.78,23.56)	0.895
Duration of infertility (years)	3 (2,6)	3 (2,5)	< 0.001
Types of infertility			0.086
Proportion of secondary infertility (%)	876 (55.65%)	828 (52.6%)	
Proportion of primary infertility (%)	698 (44.35%)	746 (47.4%)	

BMI, body mass index

Table 2 The ovarian reserve and controlled ovarian hyperstimulation of HBsAg positive group and HBsAg negative group

	HBsAg$^+$($n=1574$)	HBsAg$^-$($n=1574$)	*P*
No. of AFC	11 (7,16)	18 (14,20)	< 0.001
FSH (IU/L)	7.88 (6.49,9.5)	6.82 (5.81,8.1)	< 0.001
LH/FSH	0.5 (0.37,0.69)	0.63 (0.48,0.85)	< 0.001
AMH (ng/ml)	2.25 (1.18,3.66)	6.81 (5.56,8.24)	< 0.001
Duration of GN stimulation (days)	10 (9,12)	10 (9,11)	0.116
Total dose of GN used (IU)	1875 (1425,2325)	1600 (1300,2100)	< 0.001
No. of oocytes retrieved	7 (4,12)	14 (10,18)	< 0.001
No. of MII eggs	7 (3,11)	12 (8,16)	< 0.001

AFC, antral follicle count; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *AMH*, anti-mullerian hormone; *Gn*, gonadotropins; *MII*, mature

Table 3 The ovarian reserve and controlled ovarian hyperstimulation of HBsAg positive e antigen-negative group, HBsAg positive e antigen-positive group and HBsAg negative group

	$HBsAg^+ HBeAg^-$ ($n=1356$)	$HBsAg^+ HBeAg^+$ ($n=218$)	$HBsAg^- HBeAg^-$ ($n=1574$)	*P*
No. of AFC	11 (7, 16)[b]	12 (8, 16)[b]	18 (14, 20)[a]	< 0.001
FSH (IU/L)	7.9 (6.49, 9.5)[a]	7.73 (6.5, 9.44)[a]	6.82 (5.81, 8.1)[b]	< 0.001
LH/FSH	0.49 (0.36, 0.68)[b]	0.52 (0.39, 0.72)[b]	0.63 (0.48, 0.85)[a]	< 0.001
AMH (ng/ml)	2.2 (1.17, 3.57)[b]	2.56 (1.31, 4.18)[b]	6.81 (5.56, 8.24)[a]	< 0.001
Duration of GN stimulation (days)	10 (9,12)	10 (9, 11.25)	10 (9, 11)	0.187
Total dose of GN used (IU)	1912.5 (1431.25, 2350)[a]	1800 (1425, 2250)[ab]	1600 (1300, 2100) [b]	< 0.001
No. of oocytes retrieved	7 (4, 12)[b]	9 (4, 13)[b]	14 (10, 18)[a]	< 0.001
No. of MII eggs	6 (3, 11)[b]	8 (4, 11)[b]	12 (8, 16)[a]	< 0.001

AFC antral follicle count, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *AMH* anti-mullerian hormone, *Gn* gonadotropins, *MII* mature

Different letters (ab) on the same line indicate statistically significant differences between groups, with a *P* value < 0.05

Table 4 The multivariable logistic regression analysis of the relationship between clinical variables, HBV infection status, and decreased ovarian reserve function

Characteristics	OR (95%CI)	*P*
Age	1.224 (1.188 ~ 1.261)	< 0.001
BMI	1.019 (0.977 ~ 1.063)	0.386
Duration of infertility	0.986 (0.952 ~ 1.021)	0.412
Types of infertility (secondary infertility vs primary infertility)	0.811 (0.615 ~ 1.07)	0.139
HBsAg (positive vs negative)	103.944 (45.726 ~ 236.284)	< 0.001

BMI body mass index, *CI* confidence interval, *OR* odds ratio, *vs* versus

(44.8 ~ 230.9)) compared with the HBV-negative group ($P < 0.001$) (Table 4).

Discussion

In this study, we found that chronic hepatitis B infection in women has a significant negative impact on ovarian reserve. In terms of ovulation induction, under similar Gn days, patients with hepatitis B infection require a larger total amount of Gn, while the number of retrieved eggs and mature oocytes (MII) is reduced. However, this impact is not significantly related to the positivity of e antigen. Our study has discovered that women who are infected with HBV experience a prolonged period of infertility, which aligns with previous research findings [13, 15]. This emphasizes the potential role of HBV infection as a significant factor contributing to female infertility.

HBV has been found in the ovarian tissue including the ova, granulosa, and other cells in women with HBV infection [6, 22, 23], so there is a risk of HBV affecting ovarian function. We speculate that there may be several reasons for hepatitis B leading to decreased ovarian reserve function. Firstly, studies have found that HBsAg can replicate HBV-DNA in oocytes or embryos and be expressed at the mRNA and protein levels [24, 25]. This suggests that HBV-DNA may integrate into the chromosomes of oocytes, causing changes in the stability of genetic material and affecting ovarian reserve function. Secondly, another potential pathological mechanism of HBV infection is that the deposition of antigen–antibody complexes in infected local tissues can cause local immune reactions or inflammatory reactions, leading to the destruction of relevant functions[26, 27]. This may also be one of the reasons for the decline in ovarian reserve. Finally, research has revealed that HBV exerts a detrimental effect on male sperm quality through multiple mechanisms. These mechanisms encompass hepatitis B virus S protein can trigger the generation of reactive oxygen species, lipid peroxidation, decreased antioxidant capacity, phospholipid flipping, and activation of caspase enzymes, leading to the loss of sperm membrane integrity and abnormal sperm function[28]. Exposure to hepatitis B virus can activate the B-cell lymphoma 2 /Bcl2-associated X signaling cascade, leading to sperm DNA fragmentation, damage, and death, ultimately reducing sperm fertility [29]. Additionally, the HBs-HBs monoclonal antibody complex can reduce sperm motility and cause loss of mitochondrial membrane potential [30]. These pathogenic mechanisms may also apply to HBV-DNA integrated into ovarian tissue and oocytes.

Our research has found that hepatitis B also has a negative impact on ovulation induction: a larger total dose of Gn is required, but the number of retrieved oocytes and mature MII oocytes is reduced. This may suggest that the outcomes of IVF in HBV patients could be poorer compared to the general population. However, surprisingly, most of the current studies have not observed a significant influence of HBV on IVF outcomes[13, 14, 16, 19, 20]. We believe that there may be several reasons for this: Firstly, although HBV has a negative impact on ovarian reserve function, this impact may not be sufficient

to affect the outcome of IVF. This is because there are numerous factors that influence IVF outcomes, including embryo quality, ovulation induction protocols, endometrial conditions, laboratory conditions, and more. Secondly, HBV patients who undergo IVF have undergone proper evaluation and treatment for their HBV condition before undergoing IVF, particularly antiviral therapy. This can minimize the potential impact of HBV on IVF outcomes to the greatest extent possible. Lastly, most of the current studies on the relationship between HBV and IVF outcomes are retrospective analyses with relatively small sample sizes[14, 20]. They also lack long-term pregnancy outcome results [13, 19]. Therefore, further confirmation is needed through better-designed prospective randomized controlled studies.

There were also some limitations in our study. Firstly, it is a retrospective study, so well-designed prospective randomized controlled studies are needed to validate these results. Secondly, we did not collect data on the duration of patient infection and the level of hepatitis B virus deoxyribonucleic acid (DNA). These two indicators also play an important role in assessing the impact of hepatitis B on ovarian function[8]. Thirdly, although we matched the age and BMI of the two groups, there may still be other factors that could affect female ovarian reserve function, such as genetic factors, work environment, smoking, and alcohol consumption, among others. Lastly, the population we selected consisted of individuals undergoing their first IVF treatment, which may introduce selection bias, and further research is needed to determine if these results can be applied to the general female population. Nevertheless, our study is currently the only multicenter retrospective study with a large sample size investigating the impact of hepatitis B on female ovarian reserve function.

Conclusions

In summary, there is a relationship between hepatitis B virus infection and decreased ovarian reserve function in women of different age groups. This information is of guidance significance for HBsAg-positive women with fertility needs, as regular monitoring of hepatitis B virus levels should be accompanied by attention to ovarian reserve function. Our study also provides important insights into understanding the potential effects of chronic hepatitis B infection on female fertility and ovarian reserve. However, due to some design flaws, further research with larger sample sizes and prospective designs is needed to confirm our findings.

Abbreviations

HBV	Hepatitis B virus
IVF	In vitro fertilization
BMI	Body mass index
AFC	Antral follicle count
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
AMH	Anti-Müllerian hormone
Gn	Gonadotropins
MII	Metaphase II
DOR	Diminished ovarian reserve
HBsAg	Hepatitis B surface antigen
ICSI	Intracytoplasmic sperm injection
HBeAg	Hepatitis B e antigen
IQR	Interquartile range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03905-6.

Additional File 1: Tables S1. The ovarian reserve and controlled ovarian hyperstimulation of HBsAg positive e antigen-negative group, HBsAg positive e antigen-positive group, and HBsAg negative group in different age groups.

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Authors' contributions

All authors read and approved the final manuscript. YL, XW, and YW conceived the ideas and designed experiments; YL, YW, and YJ wrote manuscript; QL, YZ, and YL carried out experiments; YL, XW and YW analyzed experiments results. QL and YZ revised the manuscript, figures, and tables.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This was approved by the reproductive research of the Reproductive Medicine Ethics Committee of Sichuan Provincial People's Hospital (Approval number: 20240402).

Consent for publication

Consent.

Competing interests

The authors declare no competing interests.

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