Hepatitis B surface antigen in oocytes and embryos may not result in vertical transmission to offspring of hepatitis B virus carriers

Lei Jin, Ph.D., Rui Nie, Ph.D., Yufeng Li, Ph.D., Nan Xiao, Ph.D., Lixia Zhu, Ph.D., and Guijin Zhu, M.D.

Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Objective: To investigate the vertical transmission of hepatitis B virus (HBV) via embryos to children and whether HBV in embryos has an effect on the development of the fetus and pregnancy outcomes of in vitro fertilization and embryo transfer (IVF-ET).
Design: Long-term follow-up study.
Setting: Research laboratory.
Patient(s): Thirty-one couples with a hepatitis B surface antigen (HBsAg)-negative woman and HBsAg-positive man, and 41 couples with a HBsAg-positive woman and HBsAg-negative man, whose unfertilized oocytes and nonviable embryos were tested for HBV DNA, RNA, or HBsAg.
Intervention(s): HBV DNA, RNA, or HBsAg analyses in unfertilized oocytes and nonviable embryos.
Main Outcome Measure(s): HBV serologic markers analyses.
Result(s): We obtained follow-up data for 71 couples. A total of 24 babies were born, and no newborns exhibited defects at birth. Twelve babies were born to couples with HBV-positive oocytes and/or embryos. The pregnancy outcomes were not associated with the presence of HBV in oocytes and embryos. Three patterns of HBV serologic markers were screened. Twenty babies were anti-HBs-positive. Three babies were negative for HBsAg, antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), HBeAg, and antibody to hepatitis B e antigen (anti-HBe). One baby was seropositive for anti-HBs, anti-HBc, and anti-HBe at 6 months of age but seroconverted from anti-HBe-positive to anti-HBe-negative at 9 months of age.
Conclusion(s): The presence of HBsAg in oocytes and embryos may not result in the vertical transmission of HBV in the offspring of HBV carriers. (Fertil Steril® 2016;105:1010–3. ©2016 by American Society for Reproductive Medicine.)
Key Words: Embryo, hepatitis B virus, in vitro fertilization, oocyte, vertical transmission

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/leij-ivf-hepatitis-b-virus-transmission/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Hepatitis B virus (HBV) affects over 240 million persons worldwide (1). It is reported that 37.09% of HBV-infected patients are younger than 30 years of age, and 46.80% of infected patients are between 30 and 49 years of age (2). In our clinical practice, the prevalence of one or both partners infected with HBV comprises 21.75% (752 of 3,457) of all assisted reproductive technology (ART) patients. Because ART is increasingly being used for HBV-infected patients, this has raised many concerns about the safety of ART in HBV-infected patients.

Received August 5, 2015; revised December 2, 2015; accepted December 3, 2015; published online December 28, 2015.
L.J. has nothing to disclose. R.N. has nothing to disclose. Y.L. has nothing to disclose. N.X. has nothing to disclose. L.Z. has nothing to disclose. G.Z. has nothing to disclose.
Reprint requests: Rui Nie, Ph.D., Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 JieFang Avenue, Wuhan 430030, People's Republic of China (E-mail: nnrrnnrr@sina.com).

Fertility and Sterility® Vol. 105, No. 4, April 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.12.008

Hepatitis B virus is known to be present in semen, either as a free virus in seminal plasma or as an integrated genome in spermatozoa (3). In female HBV patients, HBV can infect the ovum at different stages and replicate in the ovum (4). The covalently closed circular DNA (cccDNA), which is of great significance for the replication of HBV and the establishment of infection, can also be detected in the human ovary (5). In our previous study, HBV DNA, HBV RNA, and hepatitis B surface antigen (HBsAg) were detected in oocytes and embryos from HBsAg-positive infertile couples (6). Also, fluorescence in situ hybridization

(FISH) revealed the presence of HBV DNA in oocytes and embryos from couples with at least one HBsAg-seropositive partner (7). These findings suggest that the sperm and oocytes may act as vectors for the vertical transmission of HBV to the embryos.

Whether the presence of HBV in embryos can cause vertical transmission of HBV or the HBV in embryos has an effect on the development of the fetus and pregnancy outcomes of in vitro fertilization and embryo transfer (IVF-ET) has never been evaluated. We assessed these unknowns in a long-term follow-up study in HBsAg-positive infertile couples whose unfertilized oocytes and nonviable embryos had been tested for HBV DNA, RNA, or HBsAg in our previous study (6).

MATERIALS AND METHODS

Between May 2011 and May 2014, we performed a follow-up study involving 31 couples with an HBsAg-negative woman and HBsAg-positive man, and 41 couples with an HBsAg-positive woman and HBsAg-negative man, whose unfertilized oocytes and nonviable embryos had been tested for HBV DNA, RNA, or HBsAg during IVF in our previous study. The study was approved by the institutional review board of Tongji Hospital, with informed written consent being obtained from each patient.

Data were obtained by trained interviewers using a standardized, structured questionnaire through face-to-face interviews. Maternal information included the occurrence of pregnancy, the immunization and hepatitis B immune globulin (HBIG) treatment before and after delivery, the term of delivery, the test results of HBV, and the neonatal outcome. To obtain details of treatment with ART, we searched the medical files of all the women. After full vaccination, all the children were tested for HBsAg, antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to hepatitis B e antigen (anti-HBe) (Abbott Laboratories) at 9 to 24 months of life. If the HBV markers of the children suggested a possible HBV infection, the HBV DNA loads in the plasma were analyzed quantitatively using real-time polymerase chain reaction with an HBV fluorescence quantitative polymerase chain reaction kit (PG Biotech).

Statistical Analysis

Regression analysis was performed to test female HBeAg status, male HBeAg status, the type of reproductive technology used (in vitro fertilization [IVF] or intracytoplasmic sperm injection [ICSI]), and the presence of HBV in embryos to determine the importance of each individual variable in association with ART outcome.

RESULTS

Influence of HBV in Oocytes and Embryos on the Development of the Fetus and Pregnancy Outcomes of IVF-ET

We screened all 72 HBsAg-positive couples (Table 1); one couple was lost to follow-up evaluation during the early stage of pregnancy. A total of 24 babies were born from 23 deliveries, including 14 females, 10 males, and one set of twins.

No newborns exhibited defects at birth. Of the 24 newborns, 12 were born to couples with HBV-positive oocytes and/or embryos, as follows: two couples with HBV DNA-positive oocytes and/or embryos; seven couples with HBV RNA-positive oocytes and/or embryos; and three couples with HBsAg-positive oocytes and embryos. Based on logistic regression analysis, the pregnancy outcomes were shown not to be associated with female HBeAg status, male HBeAg status, the type of reproductive technology, or the presence of HBV in oocytes and embryos.

Relationship between Serologic Markers in Children and HBV in Oocytes and Embryos

All the babies born to these HBsAg-positive couples were given three doses of vaccine (at birth, and 4 weeks and

TABLE 1

Baseline characteristics in couples with an HBsAg-positive partner.

Characteristic	Positive man (n = 31)	Positive woman (n = 41)
Woman with HBeAg positivity	0	5
Man with HBeAg positivity	4	0
No. of IVF cycles	26	33
No. of ICSI cycles	5	8
Positive detection of HBV in oocytes and embryos	12	17
No. of babies born	6	18
Miscarriage	0	4
Ectopic pregnancy	0	2
Serologic profiles of the mother before IVF		
HBsAg+, anti-HBc+, anti-HBe+, HBeAg−, and anti-HBs−	0	14
HBsAg+, anti-HBc+, HBeAg+, anti-HBs−, and anti-HBe−	0	2
HBsAg+, anti-HBc+, anti-HBs−, HBeAg−, and anti-HBe−	0	1
Anti-HBs+, anti-HBc+, anti-HBe+, HBsAg−, and HBeAg−	2	0
Anti-HBs+, HBsAg−, anti-HBc−, HBeAg−, and anti-HBe−	2	0
Anti-HBc+, HBsAg−, anti-HBs−, HBeAg−, and anti-HBe−	2	0

Note: Anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

Jin. IVF and hepatitis B virus transmission. Fertil Steril 2016.