Hepatitis B and C Virus in Assisted Reproductive Technology - A Review of Literature

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Prevalence

World Health Organisation revealed that about 5% of the population are chronic carriers of HBV. An estimated 240 million people are chronically infected with hepatitis B [1] (defined as hepatitis B surface antigen positive for at least 6 months). It is estimated that 130-150 million people worldwide are chronically infected with hepatitis C. Together these two infections constitutes 7% of world population [2]. China and India tops the list of Hepatitis B infected and most patients are unaware of chronic Infection with Hepatitis B and C.

Introduction

Hepatitis B virus belongs to Hepadnaviridae family: a family of DNA viruses with circular and incomplete double helix-strand DNA; this family of virus infects preferably hepatocytes (kidney, pancreas and mononuclear cells too). Hep B is made up by: external envelope (surface antigen) and central particle or core (nucleocapsid proteins, viral genome and a polymerase complex). Viral genotypes do prevail from A-J. 'D' genotype, being common in Mediterranean area [3].

The hepatitis C virus is a member of the flavivirus family of ribonucleic acid (RNA) viruses.

Serotypes: Hepatitis B exists as genotypes A-J and serotypes adw, adr, ayw and ayr with region specific distribution. Hepatitis C virus has genotypes 1-6 along with mixed and untypable ones; genotype 1 is the predominant one [4].

Modes of spread: Both are parenterally spread viruses; Percutaneous spread by virus containing body fluids such as saliva, urine, breast milk, semen, and menstrual fluid. Sexual Transmission with HBV- 25% and that vertical spread of HBV from mother to the offspring varies from 2-15% may be increased to 80-90% if HBeAg positive and that of HCV- vertical spread in 6% and Sexual transmission <5% which may rise to 11-16% unless co infected with HIV.

Serology

Persistence of HBsAg more than 6 months or Persistent HCV antibody more than 6 months implies chronic Hepatitis B & C respectively (Table 1 and Figure 1).

Pathogenesis

Age of the person is inversely proportional to the risk of chronic viral Hepatitis. 90% of infected neonates may develop chronic infection; while it is 25% in 1-5 years age group and 5% or less of adults [5] (Figure 2).
Why to screen

Individuals with chronic infection of Hepatitis viruses at reproductive services poses:

- Risk of transmission to uninfected partners
- Risk to Persons handling the samples at all levels
- Transmission to the child (more chances of chronic hepatitis)
- Side effects of infertility treatment on the disease
- Effect of disease on infertility treatment

- Complications of pregnancy on the disease
- Psychosocial implications of the child acquiring the infection
- Parent(s) becoming unable to care for the child due to illness/ death.

Regulations and Recommendations

Various national and international organisations like Human Fertilisation and Embryology Authority (HFEA) recommendation (1990) as amended, NICE guidelines 2013; ESHRE guidelines for good clinical and laboratory practice, The Assisted Reproductive...
Technologies (Regulation) Rules - 2010 Ministry Of Health & Family Welfare Govt. Of India have made mandatory screening for viral Hepatitis before ART.

ASRM has made some recommendations for reducing the risk of viral transmission during fertility treatment with the use of autologous gametes [6].

- Reduce viral load in the infected partner(s)
- Reduce the non-infected partner’s exposure and susceptibility to the infection
- Discuss the available scientific evidence and risk reduction strategies with both the patient and partner to provide a basis for informed consent.

Risk of transmission to uninfected partners & persons handling the samples

Knowledge of the HBV serostatus of the couple allows for Immunoprophylactic measures to be taken to reduce the risk of transmission to the partner, fetus, or new born baby. (95 % of patients will seroconvert after HBV vaccination). Precautions are to be taken against cross-contamination during sample handling and embryo cryostorage (Personal Protective Equipment’s and proper initial detection and segregation of potentially hazardous materials).

HCV RNA was detected in 89% of follicular fluids and in 25% of the culture media at day 1 from 22 IVF trials of HCV positive women, irrespective in the latter case of viral load or whether they are on antiretroviral treatment [12]. Chronic HCV infection can be treated with a combination of peginterferon and ribavirin with either boceprevir or telaprevir added in some cases. Globally, an estimated 50-95% of people treated are cured. No vaccine for HCV is currently available.

Measures to further reduce the risks of cross contamination of samples in liquid nitrogen storage [6]:

- use of specimen containers guaranteed by manufacturer to withstand freezing temperatures and thawing cycles
- use of “double bagging” or sealing techniques to prevent direct contact of cryocontainers with liquid nitrogen
- Storage of samples in liquid nitrogen vapours instead of in liquid nitrogen itself
- The use of “sperm-washing” techniques to decrease the viral load before freezing semen samples

Side effects of Infertility treatment on disease

Metformin, Progesterone preparations can exacerbate effect on compromised liver function. Gonadotrophins has no documented adverse effect.

Transmission to offspring and Effect of disease on infertility treatment

Male - Hepatitis positive

Donor insemination should be presented as the safest option; but couples persistent on autologous methods must be counselled to agree reasonable interventions aimed at reducing the transmission risk. Sperm washing by density gradient method should be done to treat HCV-positive semen before ART but those of HBV-positive males whose female partner are previously immunised against HBV need not be washed [8].

Sperm-mediated HBV genes replicate and express themselves in early embryonic cells and can transmit vertically [9]. In a study of the 18 discarded IVF embryos (nine cases) with paternal chronic HBV infection HBV mRNA by single-cell RT-PCR was detected in 1 of the 18 embryos (5.6%) but it aborted later on [10].

In the biggest prospective study with HCV infected males of Forty-seven superovulation + IUI and 38 second-level ART procedures, sperm washing technique resulted in no transmission to mothers or babies. Authors also suggested that it is not necessary to perform nested PCR to detect HCV RNA in the final swim-up [11]. Molina, et al. concluded: no seroconversions, either among the 34 neonates (tested at birth and at age 3 months), or among the 62 women treated with washed sperm during assisted reproduction programmes [8].

HBV integrate into sperm chromosomes, causing chromosomal instability and metaphase chromosome stickiness. Thus, HBV infection can induce chromosome aberrations, leading to hereditary defects in male germinal cells. HBV-infected men are shown to have lower semen volume, lower total sperm count as well as poor sperm motility and morphology (P<0.05) when compared to control individuals [12].

Gong et al. investigated the malondialdehyde (MDA) level and paraoxonase-1 (PON-1) in the serum and seminal plasma of infertile men with chronic viral hepatitis. MDA level was significantly higher, but the PON-1 remarkably lower in infertile males with chronic viral hepatitis than in the healthy controls and fertile patients (P<0.01 or P<0.05). Their levels in the seminal plasma were positively correlated with those in the serum in the infertile males with chronic viral hepatitis (P<0.01) implicating possible oxidative damage [13].

Female - Hepatitis positive

HBV vaccination aids to prevent transmission in uninfected male but risk of Mother to child transmission (MTCT) exists. With HCV, however, no vaccine is currently available. No studies reported exclusively on Females with chronic hepatitis B.

In a study evaluating susceptibility of oocyte to HCV infection, HCV RNA was associated with 17/24 (70.8 %) oocytes (6/7 after ICSI and 11/17 after conventionalIVF) and was found in 19/20 (95 %) follicular fluid samples. A weak correlation between plasma and follicular fluid HCV RNA loads (r = 0.73, P<0.001) is also noted. They also proposed that blood contamination increases HCV load in the FF and that rinsing the oocytes seems to discard the HCV RNA [14]. In another study HCV RNA was detected in 89 % of FF irrespective of the degree of blood contamination and in 25 % of the media at day 1.

A retrospective study on females with Hepatitis C showed that chronic hep C infection could alter both the reserve of small preantral follicles and granulose cell function, leading to the increased demand of FSH during ART [15].

Discordant couples vs. Infertility

Rates of two-pronuclear (2PN) fertilisation, high-grade
embryo acquisition, implantation and clinical pregnancy were reported to be lower among HBV-positive males when matched with HBV negative males undergoing ICSI; But the IVF outcomes were similar between the two groups (P>0.05) [12].

A retrospective study done in 19 couples with serospositive husbands/seronegative wives undergoing IVF with donor oocytes had lower implantation rate (26.7% vs. 40.6%; P> 0.05), and lower clinical pregnancy rate (42.1% vs. 63.8%; P> 0.05), but the difference was not statistically significant [16].

In a study with 213 HBV positive (male n=136, female n= 77) sero-discordant couples matched with 426 seronegative control groups, Couples with female HBsAg-seropositive partners had significantly lower top-quality embryo rate than control group (22.4vs.31.6 %, P<0.01). Fertilization rates in HBsAg-seropositive male and females significantly lower than the matched controls (80.2 vs. 82.8%, P<0.05 and 76.6 vs. 84.3% respectively, P<0.01). No significant difference in clinical pregnancy rates between HBsAg-seropositive and HBsAg-seronegative group [17].

In a study by Imran R. Pirwany, et al. despite comparable response to COH, and similar fertilization, and cleavage rates, couples discordant for HBV or HCV had significantly poorer implantation and pregnancy rates (7.7%, 0% respectively) compared with controls (41%) [18].

In another study, Seven of 28 men (25 %) had detectable HCV viral loads, and 14 (50 %) had elevated liver function tests, but no significant differences between embryology laboratory results for males who were only HCV sero-positive, and those who were positive for both HIV and HCV [19].

Density gradient and washing MESA or TESE samples followed by ICSI appears to suppress HCV virus detection in final suspensions of testicular and epididymal spermatozoa [20].

Both partners chronic hepatitis

Preconception counselling on the risks of sexual and vertical transmission of their infections is a must along with Adoption, as an alternate option.

Lee et al. enrolled 1676 couples undergoing their first IVF cycle and planned a comparative study of HBV sero discordant couples vs. both positive and also the negative couples; they were the first to report on the live-birth rate of hepatitis B (HBV)-seropositive couples. Though percentage of normal sperm morphology in HBV-seropositive husbands was significantly lower than that of seronegative counterparts, on-going pregnancy rate was not significantly different between couples with HBV-seropositive wives and seronegative ones (26.7 vs. 30.2 %). The on-going pregnancy rate and the live-birth rate of couples with both partners being HBV surface antigen positive was not significantly different from couples with discordant HBV’ serostatus and those couples with both partners being HBV surface antigen negative (23 vs. 29 vs. 30 %, respectively; 23 vs. 27 vs. 27 %, respectively) [21].

Pregnancy vs. Hepatitis

Pregnancy is not contraindicated in HBV or HCV infections unless there is a compromised liver function or acute exacerbations. Pregnancy neither does influence the course of the disease in chronic hepatitis nor do the diseases have an adverse effect on pregnancy outcome [22]. Hence there is no reason for declining IVF treatment in HBV or HCV patients [23]. HbsAg mother has a 10% risk of passing the infection to her offspring at the time of birth (as high as 90% if HbeAg positive) [24].

Psychosocial Implications

Counselling and education concerning safe sex practices should be provided and emphasized.

In cases where the male, but not the female, partner is infected, the couple should be explained merits of using condoms throughout fertility treatment, pregnancy, and the postpartum period.

Serial diagnostic testing of the uninfected partner is recommended throughout treatment and pregnancy and for both mother and infant during the first year after birth.

Informed consent should be explicit and as thorough as possible, emphasizing that risk of transmission cannot be completely eliminated even when specific risk reduction strategies are employed.

In-depth psychological, medical, and obstetrical care ideally should be provided by a multidisciplinary medical team.

Conclusion

Though studies have shown chronic viral hepatitis as a possible cause for male infertility and female suboptimal response in ART, there are no significant differences in live birth when compared with sero-negative couples (further prospective studies awaited).

Further Benefits of assisted reproductive technology include:

- Decreasing the risk of transmission to the partner compared with unprotected intercourse
- Decreasing the possibility that the child will be infected (though studies awaited to calculate the magnitude)
- Early intervention with prenatal/ intrapartum treatment possible to reduce transmission to the child.

References


