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Screening for blood born viruses in assisted reproduction: is annual testing necessary?

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Abstract

Purpose Screening for blood born viruses is routinely performed before fertility treatment in assisted reproduction technology (ART) clinics worldwide. It involves testing for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), among others. Identifying patients with positive viral screening allows to refer them and their partners for appropriate counseling and treatment. The need for repeat viral screening and its required frequency have never been clearly established. In Israel, viral screening is mandatory and is repeated annually. Our aim was to determine the prevalence of HBV, HCV, and HIV seroconversion in patients with negative screening upon initiation of ART treatment.

Methods A retrospective analysis of viral screening tests of all fertility patients in a single assisted conception unit between 1997 and 2015.

Results During the study period, 2844 patients were treated at our clinic, out of whom 1945 patients met the inclusion criteria. The average length of treatment was 1.61 ± 0.81 years, during which female patients underwent screening tests 2.6 ± 0.9 times, and male patients 2.3 ± 1.2 times. No case of seroconversion to any of the three viruses was noted during the entire study period, resulting a seroconversion rate of 0%.

Conclusions Primary infection with HBV, HCV, or HIV is an extremely rare event among Israeli infertile patients, and the risk for seroconversion in this population is practically nil. Annual screening of both partners leads to substantial costs and appears to be futile. Our results question the current practice and support increasing the interval between screening tests in low-risk populations.

Keywords ART · Hepatitis · HIV · Viral screening

Introduction

Sexually transmitted diseases (STDs) are of major concern in the field of assisted reproduction. Of paramount importance are the blood born viruses (BVV) human immunodeficiency virus (HIV) and hepatitis B (HBV) and C (HCV) viruses [1]. These pathogens, which may cause incurable and even fatal infections, can be transmitted through insemination procedures and from infected mothers to their offspring. In case of infection diagnosed prior to assisted reproduction technology (ART) treatment, appropriate precautions should be undertaken to minimize the risk of viral transmission to partners and offspring, and to protect health care providers, as well as the gametes and embryos of other patients being treated at the same clinic [1, 2]. The recent availability of sensitive and precise diagnostic tests has allowed early detection and monitoring of viral infections, and new antiviral drugs have made it possible to cure or manage many of these infections [1]. Carriers of viral diseases are now living healthier, longer lives, and many choose to have children. Therefore, infected patients can receive appropriate counseling and, when necessary, antiviral therapy before embarking on conception. Detecting chronic viral diseases before commencing assisted reproductive technology (ART) treatments is, therefore, of major importance.

For these reasons, screening for BVV has become a routine practice in most ART units worldwide. In most fertility centers

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in Europe and North America, patients willing to undergo assisted conception are required to be screened for HIV, HBV, and HCV. However, national guidelines on the matter vary widely. The need for repeated BBV screening and the required frequency of such testing have never been clearly established. In some countries, screening is performed only once before initiating treatment, while in others, it is repeated either once a year, every 2 years, or before the initiation of every treatment cycle. Because of the huge economic and administrative burden involved in repetitive screening for the individual and health care providers, an intense debate regarding the required frequency of screening for STDs has taken place and is still ongoing [3, 4]. In Israel, annual screening for HIV, HBV, and HCV is mandatory. To evaluate the validity of the Israeli screening policy, our aim was to study the prevalence of HIV, HBV, and HCV seroconversion in patients with negative screening upon initiation of ART treatment.

Materials and methods

A retrospective analysis of all BBV-screening tests in a single university affiliated ART clinic, during an 18 year period between 1997 and 2015, was conducted. Data were collected from the patients' medical records. Since 1997, every patient treated in our clinic and her partner have been required to perform viral screening tests annually according to regulations of the Israeli Ministry of Health. In case a patient returns for treatment after cessation of more than 1 year, all tests were repeated. Two groups of patients were included in the study; the first group consisted of patients treated for > 1 year, and the second group consisted of patients returning for treatment after an interval of > 1 year, usually after pregnancy and live birth.

The following test results were recorded for both patient and partner, whenever applicable: Hepatitis B surface antigen (HBsAg), anti-HCV antibodies, and anti-HIV antibodies. Patients who were known carriers of viral disease upon initiation of treatment were excluded. Seroconversion was defined as a positive result for any of the above tests in patients who were sero-negative on their first screening before initiating treatment. Seroconversion rate was defined as the proportion of subjects with seroconversion among all study patients. The study was approved by the Institutional Review Board. Due to the retrospective nature of the study, informed consent was deemed unnecessary.

Results

During the study period, 2844 patients were treated at our unit; out of whom 1945 patients met the inclusion criteria, including 974 women and 971 men. Mean age of female patients was 33.86 ± 5.6, and 530 returned to treatment after a break. The average length of treatment was 1.61 ± 0.81 years. Including returning patients, female patients performed screening tests 2.64 ± 0.99 (range 2–8) times and male patients performed screening tests 2.37 ± 1.22 (range 1–8) times. The discrepancy in the number of tests between females and males results from the fact that there was a small proportion of female patients using donor sperm. Table 1 presents the number of tests performed in women and men.

Table 1 Number of viral screening tests performed in patients undergoing fertility treatments

Number of tests	Women, *n* (%)	Men, *n* (%)
0	0	62 (6.4)
1	0	78 (8.0)
2	593 (60.9)	494 (50.9)
3	223 (22.9)	193 (19.9)
4	101 (10.4)	89 (9.2)
5	33 (3.4)	34 (3.5)
6	18 (1.8)	15 (1.5)
7	5 (0.5)	5 (0.5)
8	1 (0.1)	1 (0.1)
Total	974 (100)	971 (100)

Table 2 Incidence of positive viral screening tests in patients undergoing fertility treatments

Virus	No. of individuals tested	No. of positive test before treatment initiation, *n* (%)	No. of female seroconversions	No. of male seroconversions
HBV	1945	20 (0.010)	0	0
HCV	1945	17 (0.008)	0	0
HIV	1945	0	0	0

Table 2 presents the number of tests and the number of infected individuals according to each virus. The incidence of a positive screening test before the initiation of treatment was very low; 0.01% for HBV and 0.008% for HCV. There were no cases of HIV-positive tests, as in Israel, HIV carriers are referred to a single designated ART clinic. No case of seroconversion to any of the viruses was noted during the entire study period, resulting a seroconversion rate of 0%.

Discussion

The results of our study indicate that during a period of 18 years, there were no cases of HIV, HBV, or HCV seroconversion among Israeli patients or their partners undergoing fertility treatments at our clinic. Our results are in agreement with the previous studies performed in Europe [5–8], and

indeed, once again demonstrate that with current laboratory practice, the risk of seroconversion in single females or cohabitating couples in a low-risk population is practically zero. These facts and figures should be taken into consideration while establishing the guidelines for BBV screening in the setup of ART.

In Europe, ART is currently covered under the European Union Tissues and Cells Directive (EUTCD; EC/2004/23), a legal document originating from the European Union's public health program. The Directive covers donation of all tissues and cells within the EU (except blood and blood products). In October 2009, the Commission stated that in terms of the Directive, all ART patients must be tested for HIV, hepatitis, Human T-lymphotropic virus (HTLV), and syphilis prior to each treatment and that this is not open for national interpretation. Many couples undergo a series of tests once a year instead of every "donation". However, according to the Directive, like any organ or tissue donations, testing should be done before each treatment, regardless of the time interval between consecutive cycles.

An ESHRE position paper published in 2007, suggested that screening can be performed within 30 days prior to treatment, and is valid for 24 months if negative [9]. Since there has been no single documented report of viral transmission in the area covered by the Directive [3, 4], ESHRE's comment was that the ART field should have a separate specific Directive, given that ART is different in its specifications compared to tissue or organ donations [10]. The European Union Tissues and Cells Directive is currently being re-evaluated [11].

In the meanwhile, because of extremely low, but yet undetermined, risk for seroconversion in sero-negative individuals undergoing ART, and because of the huge economic and administrative burden involved with repetitive screening for the individuals and health care providers, an ongoing debate has started regarding the necessary frequency of screening for BBVs [3–6]. Many national authorities are in line with ESHRE and see this interpretation of the Directive as excessive and not medically or scientifically justified. There seem to be different interpretations and practices regarding the period of validity at the national level. For example, in Ireland, repeat testing is required prior to each and every ART cycle, while in Finland, repeat testing is required every 12–24 months [3, 4]. In Denmark, viral screening is valid for 24 months and most clinics in the UK and France test annually [3, 4]. In the United States, The Practice Committee of the American Society for Reproductive Medicine recommends viral screening for couples proceeding to ART, but does not specify the frequency of repeat screening [2].

There have been several studies that evaluated the outcome of repeated screening for BBV and seroconversion rates in different ART populations. Pepas et al. [6] examined the rate of seroconversion of HBV, HCV, and HIV within 12 months in an ART clinic at an area of high-risk population in London, UK. Out 422 patients who underwent repeat screening none has seroconverted within 3 years. Hughes et al. determined the incidence of BBVs in patients presenting for ART treatment in Dublin, Ireland, and assessed the likelihood of seroconversion after an initial negative screen [5]. Between 1998 and 2009, a total of 79,291 tests were performed in over 12,500 patients. In this population, the incidence of HBsAg was 0.28%, Hepatitis B core antibody 3.32%, HCV antibody 0.33%, and HIV 0.007%. For over 6500 individuals who were tested and re-tested for all three viruses, no seroconversions were reported. Wingfield and Cottell [3] analyzed viral testing results from 13,717 individuals seen at seven Irish fertility clinics between 2007 and 2009. Based on initial testing, no patient was positive for HIV, while the incidence of positive tests for HBsAg was 0.13%, Hepatitis B core antibody 1.3%, and 0.12% had antibodies against hepatitis C. Of those patients who went on to have fertility treatment, repeat testing over the course of treatment found no new cases of HIV or hepatitis infection. Hughes et al. [5] also calculated the financial implications of the Irish BBV screening imposed practice (screen at each cycle) to be €1,440,000 annually for Ireland and €240 million at the European level. Annual screening could lead to cost savings of €960,000 for Ireland and €260 million for Europe. It was suggested that based on the above measured negligible risk of seroconversion after an initial negative screen in cohabitating couples participating in an ART program, current legislation requiring screening of couples at each procurement of cells in the ART setting is not clinically justified [3–5].

The prevalence of HIV carrier state in Israeli adults for the year 2016 has been reported to be 4/100,000 or 0.004% [12]. Age-adjusted seroprevalence of HCV in Israel has recently been estimated at 0.52%, with substantially higher rates among immigrants from the former Soviet Union and injecting drug users [13], and the corresponding figure for chronic HBV infection has been estimated at 0.96% (0.93–0.99) [14]. This incidence is lower than in most Western European and North American countries [14, 15] and is actually among the lowest reported in the world; yet, differences exist in Israel between sub-population groups. It is difficult to estimate the exact cost of viral testing in Israel, because patients perform such tests through their medical insurance providers, and there is no disclosure of the pricing from the different centralized laboratories. It can be assumed that the estimation of Hughes et al. [5] of an average cost of about €20 per test, an annual cost per patient of €60 and €120 per couple, the cost of screening with every cycle of the 37,270 cycles performed in Israel in 2016 would be €2,236,200 for the female patients only, and this figure would be doubled once the cost of the male partner screening is included in the analysis.

The evidence presented in our paper clearly demonstrates that repeat screening on an annual basis is unnecessary in a low-risk population and is actually a waste of the very limited resources of our health system. Furthermore, good laboratory practice, advances in sample preparation, and the use of high security cryostorage methods have significantly reduced the risk of cross contamination in the laboratory [1]. Therefore, when up-to-date best practice ART procedures for gamete and embryo processing are employed, cross contamination in the ART facility or horizontal or vertical transmission to a partner or neonate is unlikely, and indeed has never been documented [3–5]. A better strategy, in our opinion, would be to perform initial viral screening, then during treatment, to conduct repeated testing according to the regional or national risk level which should be determined specifically for each clinic. In a low-risk environment such as ours, the frequency of screening could be safely reduced to once in every 2 years. In a high-risk environment, such as certain regions in Africa [16], the frequency of screening should be high. The following additional measures should also be employed even in low-risk populations: (1) couples should be evaluated periodically about any changes in their risk factors for BBVs (e.g., IV drug use, a recent tattoo, or risky sexual behavior) and re-tested if necessary. (2) Repeat BBV screening should be done upon the initiation of pregnancy, a safety measure which is routinely done anyway in many clinics. We encourage ART clinics worldwide to perform similar analyses, to gather the medical and scientific evidence that could help convince the authorities that the testing policies for BBVs should be re-evaluated.

The strength of our work lies in the length of the observation period (18 years), which to the best of our knowledge, is the longest observation on a cohort of ART patients reported in this context. Several limitations, however, must be acknowledged; first, our study included patients treated in a single fertility unit is Israel, which weakens its generalizability. Second, we did not include individual information regarding risk factors for BBV infections among our patients in the analysis. Third, although there was no sero-conversation for HBV during the study period, it cannot be excluded completely. HBsAg is detected approximately 6 weeks after infection and becomes negative after 6 months. Hence, a possible infection is not completely excluded.

In conclusion, seroconversion to HIV, HBV, and HCV is an extremely rare finding among Israeli infertile patients. Annual screening of both partners leads to substantial costs and appears to be futile. Our results question the current practice and support increasing the interval between screening tests in low-risk populations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent For this type of study, formal consent is not required.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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