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Human Immunodeficiency virus(HIV) & medically assisted reproduction (MAR)

Human Immunodeficiency virus (HIV)

THE PREVALENCE OF HUMAN IMMUNODEFICIENCY VIRUS :There were an estimated 38 million people living with HIV at the end of 2019.

the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient

There are two major viral species of HIV known, HIV-1 and 2. The HIV-1 strain is the more virulent, the most prevalent .

How should testing of HIV status prior to medically assisted reproduction be performed?

- HIV-1 RNA, p24 antigen, HIV-1 IgM antibody, and HIV-1 IgG antibody
- HIV fourth-generation test
- nucleic acid test (NAT)
- HIV self-testing and rapid tests

HIV testing is mandatory as a preventative measure to reduce the risks of transmission to partners

What are the risk of HIV transmission through vaginal/anal intercourse?

- Among couples where the index case has suppressed viral load, 0 transmissions over 1327 person-years were identified
- in the study by Quinn et al. (2000) the rate of HIV-1 transmission was zero among the 51 couples in which the HIV-1–positive partner had undetectable serum levels of HIV-1 RNA or less than 1500 copies/ml
- Deschamps et al. (1996) reported that the incidence of HIV infection was 1.0 per 100 person-years for persons who always used condoms and 6.8 per 100 person-years for persons who used condoms irregularly or not at all

Strong

- Human immunodeficiency virus (HIV)-1 serodiscordant couples should be informed that there is a risk of sexual transmission of the virus to the unaffected partner. To reduce this risk, couples must be advised to use barrier contraception and seek active therapy to reduce viral load
- In individuals testing positive for HIV-1, antiretroviral therapy can suppress viral replication. When undetectable viral load in blood has been achieved, there is good evidence that the risk of horizontal transmission due to unprotected intercourse is minimal

Is there a threshold below which transmission of HIV is unlikely?

- no HIV transmission events occurred in discordant heterosexual couples if the partner testing positive for HIV was treated with antiretroviral therapy and had a viral load below 400 copies/ml (Attia et al., 2009)
- Vertical transmission: *We were unable to retrieve studies that investigated the maternal viral load before MAR and the risk of vertical transmission to the new-born.*

Strong

- Commencement with medically assisted reproduction (MAR) in patients positive for HIV-1 or 2 should be a joint decision between the infectious disease specialist and the fertility specialist
- All patients testing positive for HIV, wishing to have a child should be counselled about the risk of horizontal and vertical transmission. In the case of the male testing positive for HIV, antiretroviral therapy can reduce the viral load in blood and semen to undetectable levels, allowing the possibility of natural conception. Reproductive counselling should include fertility and antiretroviral covariates
- In the case of the female testing positive for HIV-1 or 2, and even with undetectable viremia, the possibility of viral vertical transmission should be discussed prior to MAR treatment

Should IUI,IVF or ICIS be preferentially used for MAR in HIV infected couples?

- In 15 studies, 12 studies reported on serodiscordant couples with a male partner testing positive for HIV-1 and 7 with a female partner testing positive for HIV-1. The clinical pregnancy rate was 30% (95CI: 25%-35%) in couples with male partners testing positive for HIV-1 (n=780) and 16% (95CI: 13%- 20%) for couples where the female partner tested positive for HIV-1 (n= 253). Zero HIV-1 transmission was observed in 1254 IVF/ICSI cycles in serodiscordant couple with a male partner testing positive for HIV-1 (Barnes, et al., 2014)

- Evidence from 2 structured reviews, although having overlapping studies in their results, showed that the pregnancy outcomes in IUI are lower compared to IVF/ICSI cycles as is the case in patients testing negative for HIV-1. The decision on which type of MAR treatment is chosen, is to be solely based on the fertility status of the couples.
- The systematic review of Barnes (Barnes, et al., 2014), showed that in women on antiretroviral therapy and testing positive for HIV-1, 32%-75% suffered tubal factor infertility (5 studies), 8%-12.5% ovarian factor infertility (2 studies), 2% were diagnosed with endometriosis (1 study), 10%-37% had partners with male infertility (5 studies) and 12%-20% were 'other' or unknown factors (2 studies).

- There is no preferred MAR method of choice based on infection status of the patient or the couple. The current evidence shows that safety is equal in all MAR techniques after specific semen processing.
- All evidence in the reported papers, showed zero seroconversion in female partners of serodiscordant couples where the male tested positive for HIV-1 and no vertical transmission has been shown in the babies born from MAR in couples testing positive for HIV-1.

Strong

- HIV infection status is not a reason to deny MAR treatment.
- The cause of infertility should dictate the specific technique (IUI/IVF/ICSI) used for MAR in couples where one or both partners test positive for HIV.

Can HIV DNA be detected in Oocytes/ sperm/ placenta?

- An observational study, including semen of 22 male patients testing positive for HIV-1 compared to 12 male persons testing negative for HIV-1, observed that in 75% of all semen samples tested; T cells were most commonly infected with HIV-1, followed by macrophages in 38% of all samples. Viral DNA was, in this study, never detected in motile spermatozoa (Quayle et al., 1997)
- A basic research study where semen samples of 17 male persons testing negative with HIV-1 were co- incubated with HIV-1, observed the binding of HIV-1 to the plasma membrane of the spermatozoa and the presence of virus-like particles in vacuoles in the apical nuclear region of the spermatozoa (Dussaix et al., 1993).
- An original basic research study were 100 oocytes from 15 female patients testing negative for HIV-1 were co-incubated with HIV-1, found no cell associated HIV-1 antigen neither virus-like particles in any of the experiments. The putative HIV-1 receptor (GalAAG) could not be detected on the oocytes (Baccetti et al., 1999).

Placenta

- In a prospective cohort study, including 37 women testing positive for HIV-1 (39 pregnancies), HIV-1 was detected in 12/37 placentas with immunohistochemistry (IHC), staining synctiotrophoblast and villous mesenchymal cells. In addition, 3/18 placentas tested positive for HIV-1 by PCR. However, only for 1 placenta, the tests were concordant (Dictor et al., 2001
- Another cohort study, investigating the placentas 75 women testing positive for HIV-1 reported that no HIV-1 protein positive cells were found in the frozen sections of the placentas by IHC. Furthermore, in- situ hybridisation (ISH) also showed no HIV-1 proteins, regardless of the clinical status of the mother (Peuchmaur et al., 1991).

- The virus particles were found between the plasma membrane and the outer acrosomal membrane in the sperm head, the neck or in the mitochondrial districts. The particles did have the diameter of a virus particle, but they never showed a nucleoid-like structure, hence the authors concluded that viral particles were found in the sperm cytoplasm and these represented infecting but not replicating virions
- Seminal vesicles, macrophages and T-cells are most probably the carriers of HIV particles in a semen sample. Semen processing techniques are therefore necessary to eliminate these contaminating cells (Quayle, et al., 1997). Although there is a theoretical risk for introducing HIV particles through ICSI, the probability is very small with processed semen.

- There are very few studies reporting on the RNA/DNA detection in oocytes from female patients testing positive for HIV. Viral DNA and RNA cannot be detected in oocytes when co-incubation experiments with HIV are performed. No observation of virus-like particles in the oocytes were found, whereas similar experiments using sperm, did detect virus-like particles in the spermatozoa (Baccetti, et al., 1999). HIV receptors could not be detected on oocytes
- Oocytes could get infected with HIV upon performing ICSI, however the study of Steenvoorden et al. (2012) showed that this risk, although theoretically possible, is highly unlikely to occur when using a processed semen sample of a patient testing positive for HIV (Steenvoorden, et al., 2012).

- HIV-1 viral particles can be detected in spermatozoa of male patients testing positive for HIV, and the majority of infected cells in semen are probably contaminating leucocytes in the semen, therefore special laboratory techniques for semen processing are needed to reduce the viral content
- HIV-1 RNA/DNA cannot be detected in oocytes of female patients tested positive for HIV, therefore no special laboratory techniques are needed for processing of their oocytes.

There is no evidence of HIV nucleic acid integration in the genome in human spermatozoa. Semen can be prepared to collect spermatozoa free from HIV RNA and DNA and used for MAR. Similarly, HIV RNA/DNA has not been detected in human oocytes.

Dose HIV/treatment before MAR impact the outcome of medically assisted reproduction?

- Male infected :An age-matched control study compared outcomes from 43 serodiscordant couples with a male partner testing positive for HIV-1 (55 ICSI cycles) with 50 age-matched couples testing negative for HIV-1 (55 ICSI cycles). There was no significant difference in clinical pregnancy rate per ET (45% vs. 40%) or miscarriage rate per ET between serodiscordant couples and the control group. No seroconversions were observed in the female partners and all 17 babies born from serodiscordant couples were HIV-1 negative, 3 months after their birth (Sauer and Chang, 2002).

- Female infected :A systematic review and meta-analysis summarized publications on outcomes of IVF/ICSI from 10 studies. a lower pregnancy rate was observed for HIV+ women and in 4 case control studies, there was no significant difference in pregnancy outcome for HIV+ women compared to seronegative control couples (Marques et al., 2015)

- Serodiscordant couples with a male partner testing positive for HIV-1 should be informed that the efficacy of medical assisted reproduction is not impacted compared to HIV seronegative couples(Strong)
- Serodiscordant couples with a female partner testing positive for HIV should be informed that the efficacy of IVF/ICSI could be reduced compared to HIV seronegative couples

What is the best technique for semen processing to reduce HIV viral load?

- In the cohort study of Zamora et al. (2016), 269 semen processing procedures were performed in 183 serodiscordant couples with a male partner testing positive for HIV-1. The semen was used in 234 completed ICSI cycles. Semen was processed via triple density gradient (90-70-45%) centrifugation followed by swim-up. Even after this preparation, 1.86% of the samples tested positive for HIV-1 (Zamora et al., 2016).
- The study of Persico et al. (2006) including 55 male patients testing positive for HIV-1 where the semen was prepared through a density gradient (90-47%) followed by swim-up. HIV-1 RNA was found in 2% of the samples after density gradient and all samples tested negative for HIV-1 after the swim-up procedure (Persico et al., 2006).

Strong

- The technique recommended for processing ejaculated semen for males testing positive for HIV is to perform a discontinuous density gradient centrifugation followed by 2 semen washing steps, followed by swim-up.

IS THERE A NEED FOR PCR TESTING OF POST-WASHED SPERM?

Strong

- Regardless of the semen processing technique used, the post-preparation sample that is going to be used in MAR should be HIV PCR tested
- Only a HIV negative tested sperm sample should be used for MAR in serodiscordant couples.

IS THERE A NEED FOR SEMEN PROCESSING WHEN BOTH THE MALE AND FEMALE ARE INFECTED?

Good laboratory practice regarding semen processing should be applied irrespective of whether one or both partners are testing positive for HIV.

DOES THE PLASMA VIRAL LOAD CORRELATE WITH HUMAN IMMUNODEFICIENCY VIRUS DETECTION IN SEMEN?

- Advanced semen processing is recommended for male patients testing positive for HIV, regardless of the viral load in the serum and therapy status.

WHICH INTERVENTIONS CAN BE USED TO REDUCE/AVOID VERTICAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TO THE NEW-BORN?

- Caesarean section is recommended in women with detectable HIV viral load
- Females testing positive for HIV should refrain from breast-feeding when and where safe nutritional alternatives exist
- CNP is recommended for neonates born to mothers testing positive for HIV.

HIV	Male testing positive		Female testing positive		Couple testing positive	
BEFORE MAR	Consult with infectious disease/liver disease specialist					
	Undetectable viral load	HIV detected in blood	Undetectable viral load	HIV detected in blood	Undetectable viral load (female)	HIV detected in blood
		Risk of HT	Risk of VT	Risk of VT + HT	Risk of VT	Risk of VT + HT
DURING MAR	IUI, IVF or ICSI depending on infertility work-up					
	Specific semen processing* and semen HIV PCR testing recommended		Standard oocyte processing		Specific semen processing* and semen HIV PCR testing recommended	
AFTER MAR			Caesarean section recommended if detectable HIV viral load			
	Breastfeeding = option		Breastfeeding not recommended			
			CNP			

Thank you