

Dr. Abha Majumdar

Director , Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA



Graduation & post graduation in Obs & Gyne: Agra Medical College;
Fellowship of International College of Surgeons FICS in 1994.

Awarded **Presidents Medal** for Best Medical Graduate for 1975.

Felicitated by **Dr. B.C Roy's prestigious award** in 1999, for outstanding contribution towards medicine and field of specialty.

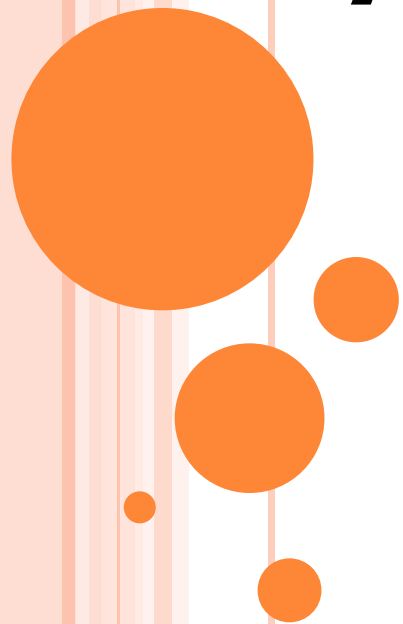
Awarded **Bharat Vikas Ratan Award** by nations Economic Development & Growth Society 2002, **Chiktsa Ratan Award** a certificate of excellence in Medical Science by International Study Circle on 25th July 2007.

Felicitated by S.N.Medical College for outstanding contribution to the specialty. Appointed by **National Board to award Fellowship in Reproductive Medicine**

Attached to Sir Ganga Ram Hospital, New Delhi since 1987. Presently Senior Consultant and Director of the Unit of IVF and Reproductive Medicine SGRH. This hospital provides comprehensive infertility services under one roof as one of the most prestigious and largest center of northern India.



ART & VIRAL INFECTIONS



CONCERN WITH VIRAL INFECTIONS IN ART

- These pathogens may cause incurable often fatal infections
- Sexually transmitted (STIs) between partners
- Can be transmitted to health workers
- Can be vertically transferred from mother to fetus or to new born
- May lead to major malformations, malignancies, IUGR in neonates apart from life long infection



CATEGORIES OF VIRAL STIs ACCORDING TO COMMON OCCURRENCE & VIRULENCE

○ Category 1:

- HIV 1 & 2, hepatitis B (HBV), hepatitis C (HCV)

○ Category 2 of less common and less virulent STIs

- hepatitis A (HAV),
- human T-cell lymphotropic virus (***HTLV1 and II***)
- human papilloma virus (HPV)
- several members of herpes virus family such as Epstein Barr virus (EBV), ***Cytomegalovirus (CMV)***, herpes simplex virus 2 (HSV-2) and human herpes simplex (HHV)- types 6 and 8



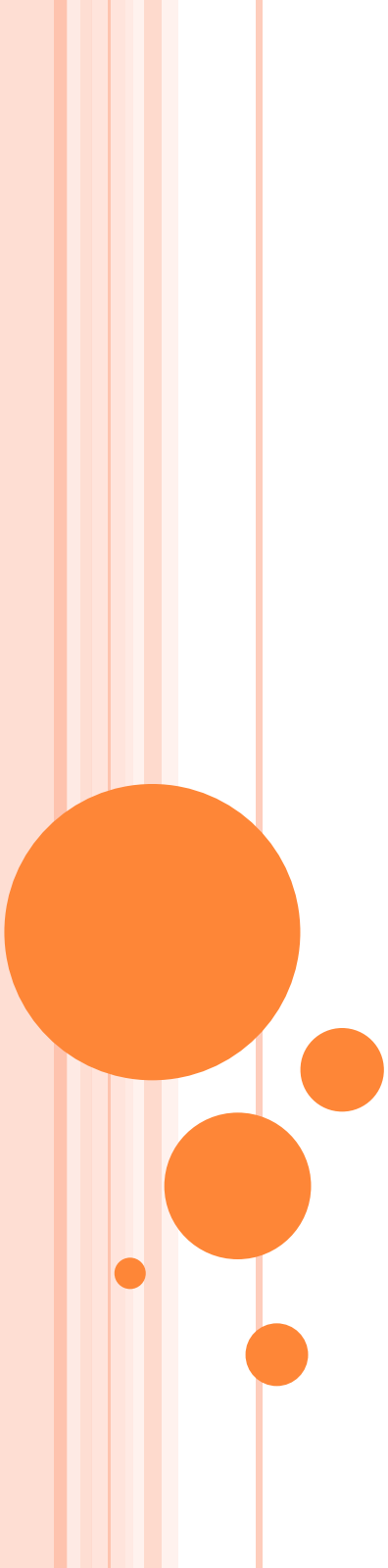
STIs can cause life long chronic infections

2 decades of intensive research have not provided cures

Substantial body of information has been produced to form risk reduction strategies

- Early detection with precision
- Monitoring of progression or regression of disease
- New anti- viral drugs available

HIV infected individuals are now living longer and healthier and choosing in increasing numbers to have children thus seeking help of fertility services to reduce risk to their partners and off-springs



Ethics committee of ASRM:

Fertility services cannot be withheld ethically from individuals with chronic viral infections including HIV, if a center has the resource to provide care or should refer to a place with such facilities

RISK OF VIRAL INFECTIONS AND ART

ART has the risk of transmission of virus to women, the child and health workers

Concern about inadvertently transferring infection into female by donor semen

In discordant couples with man positive: risk of transmission by semen or sperms to partner

In female positive no risk of transmission to partner but risk to child of vertical transmission

ART exposes the health personnel to the risk of STIs



ART IN DISCORDANT COUPLES

Based on scientific principles and clinical experience

Reduce viral load in infected partner before ART

Reduce exposure & susceptibility of non-infected partner

Frank detailed discussion with informed consent



ART IN DISCORDANT COUPLES

- Risk of transmission lowest in sexual contact with peripheral viral load $<10,000$ copies/ml
- Most viruses found primarily in WBCs and as cell free viruses in semen thus semen preparation techniques and ART effective
- Treat associated STI or genital inflammation prior to ART as semen viral load may be much more than peripheral viral load.
- Use HAART to reduce viral load in semen.
- Reduce trauma to cervix and uterus during insemination



TRANSMISSION RISK REDUCTION STRATEGIES IN ART

For infected partners going for conception with own gametes

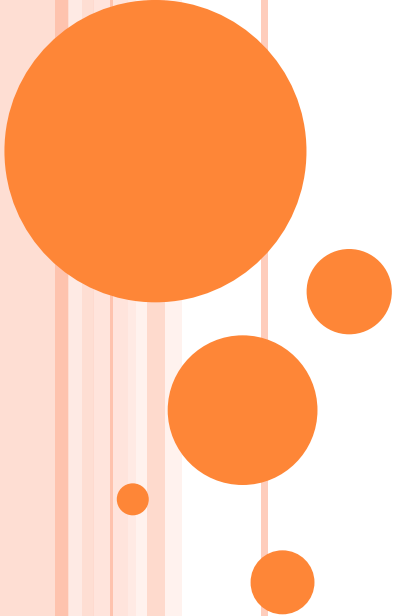
- Samples from viral carriers processed in separate lab or designated place in the lab with separate equipment to be utilized
- Separate storage tanks for cryopreservation as HIV, HCV, HBV etc can survive in liquid nitrogen
- Use of double bagging or sealing techniques to prevent direct contact of cryo-containers with liquid nitrogen
- Storage in liquid nitrogen vapor instead of liquid nitrogen itself
- Sperm washing before freezing semen samples



TRANSMISSION RISK REDUCTION STRATEGIES IN ART

For infected partners going for conception with own gametes ***Sperm washing***

- ❑ Density gradient centrifugation followed by swim up to separate motile sperm from HIV, HCV and other viruses in free form or in somatic cells like- WBC or epithelial cells
 - ❑ Quantitative assessment of HIV in sample before and after sperm wash as > 99% of HIV is removed although 5 to 10% samples contain residual virus
 - ❑ Routine testing by PCR for HIV and HCV in washed semen sample for complete prevention of infection in woman
- 



HIV 1 AND 2

HIV 1 is more virulent, severe, rapidly developing and infective than HIV 2 and most untreated individuals die faster .

RISK OF HIV TRANSMISSION

- Rate of HIV hetro-sexual transmission is relatively low: 1 in1000 unprotected sexual acts
- Predisposing factors: genital tract infections and ulceration, sexual practices that induce trauma or bleeding
- Lack of male circumcision



Reproductive Options for HIV-Concordant and Serodiscordant Couples (Updated September 14, 2011) (GLChunk_153)

Available at <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf>.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion



USA FDA approved guide lines

- For serodiscordant couples wanting to conceive, expert consultation recommended so that approaches can be tailored to specific needs, which may vary from couple to couple **(AIII)**.
- Partners to be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- For an HIV-infected female with an HIV-uninfected male partner, the safest conception option is artificial insemination, including the option of self-insemination with partner's sperm in peri-ovulatory period **(AIII)**.

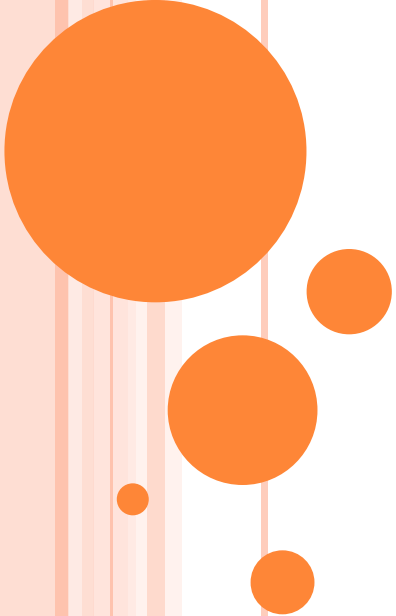


- For HIV-infected men with uninfected female, use of sperm preparation with either IUI, IVF or ICSI should be considered if using donor sperm unacceptable **(AII)**.
- In serodiscordant couples wishing to conceive
 - Initiate antiretroviral therapy for HIV-infected partner if CD4 count ≤ 550 cells/mm³ **(AI)**.
 - CD4 counts >550 cells/mm³, consider initiation of ART **(BIII)**.
 - Maximal viral suppression recommended if therapy has been started **(AIII)**.
- Data are insufficient currently to recommend peri-conception administration of antiretroviral as prophylaxis for HIV-uninfected partners to reduce the risk of sexual transmission **(AIII)**.



HIV PREVENTION AND SCREENING FOR ART IN WOMEN

- Experimental Approaches:
 - Pre exposure prophylaxis (PREP) with antiretroviral drugs (tenofovir)
 - Locally applied vaginal estrogen cream
- Uninfected partner to be tested at 3 months interval during treatment & pregnancy
- If infected prevention of vertical transmission: HAART, elective LSCS, avoidance of breastfeeding, neonatal prophylaxis.



VIRAL HEPATITIS

B, C and A

VIRAL HEPATITIS AND ASSISTED REPRODUCTION

- Transmission of HBV and HCV : main area of research
- The concern over laboratory infection in ART clinics has grown: case report of transmission of HCV from infected patient to 2 non-infected patients undergoing IVF within the same clinic in the same period
- Development of additional regulations for ART in hepatitis patients
- In 2001 emergence of 'viral risk' laboratories in France to treat serodis-cordant couples wanting to go for ART



Risk factors for Hepatitis B (15–17) and Hepatitis C (27–30).

1. Persons of Asian or Sub-Saharan African descent.
2. History of IV drug use.
3. History of sexually transmitted diseases.
4. Multiple sexual partners.
5. History of hemodialysis.
6. Health care worker.
7. History of solid organ transplant.
8. History of transfusion of blood or blood products.
9. Prisoner.
10. Infant born to an HBsAg or HCV Ab-positive mother.
11. Sexual partner of HBV or HCV infected person.
12. Sexual partner of an IV drug user.
13. Tattoos or body piercing.

HBV POSITIVE MALE/COUPLE

- Most common infectious disease in the world: 350 million people world wide are HBV carriers
- Risk to uninfected partner: approximately 25% of regular sexual contacts
- Uninfected partner – immunize, confirm immunity by anti HbsAg antibody >10mIU/mL & then start ART
- Sperm washing with aim to reduce viral load not necessary. (But can reduce viral load before cryopreservation)
- Woman infected: immuno-prophylaxis within 12 hours to new born

HCV

- HCV status usually assessed with ELISA/RIBA
- Most sensitive: HCV RNA PCR

Clinical indication for HCV-PCR testing.

Indeterminate RIBA results

Chronic hepatitis with negative HCV antibody

Normal ALT levels with positive HCV antibodies

Acute HCV infection

Fulminant hepatitis C

Patients refusing liver biopsy

Pregnant women who have HCV antibodies

Newborns exposed to HCV

Monitor response to antiviral therapy

ASRM Practice Committee. Hepatitis and reproduction. Fertil Steril 2008.

HCV

- No vaccine for HCV
- Highly pathogenic: 80% chronic liver disease, 35% cirrhosis, 5% hepato-cellular carcinoma
- Small but measurable risk of transmission via semen
- Risk reduced by sperm preparation
- Hepatitis A and B vaccination recommended for all persons with HCV if they are sero-negative for either A or B
- Risk of vertical transmission from mother: $>10^6$ copies/mL
- Breastfeeding allowed.



HEPATITIS C

In infertility practice routine screening may be offered to all couples to help identify asymptomatic women/men who may need therapy before ART or conceiving

- Recommendation: Either partner chronically infected
 - Anti- viral pretreatment: 48 weeks to reduce viral load
 - Avoid pregnancy for 6 months after therapy of either partner undergoing Rx. (Use two methods of contraception Cat X drug)



Counseling infertile couples in which one partner is HCV positive.

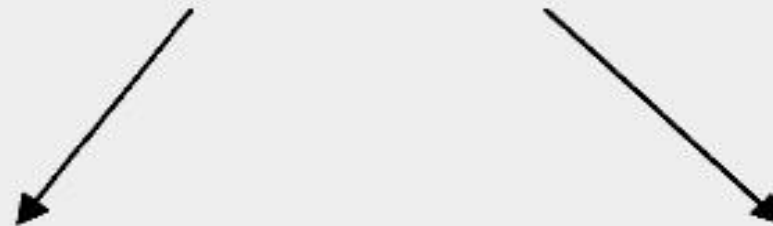
Confirm HCV status with RIBA and obtain viral titers

Test partner for HCV status

Vaccinate patient and partner against HAV and HBV, if nonimmune

Check HIV status

Obtain liver function tests and gastroenterology consult



Patient and partner are HCV positive



Patient and partner are discordant



Counseling infertile couples in which one partner is HCV positive.

Continued

Patient and partner are HCV positive



**Consider therapy when viral
titers are low**

**Consider interferon/ribavirin therapy
before fertility treatment to decrease the
risk of transmission to the fetus**

Patient and partner are discordant



**Counsel about controversial issue
of sexual transmission**



**Consider IUI therapy to possibly
decrease the risk of transmission**

HAV

Vaccine: Two dose 6 months apart.



Risk of transmission to and from health care workers.

Disease	Risk of transmission to and from health care workers
Hepatitis A	Minimal risk of transmission; use standard precautions.
Hepatitis B	The risk of transmission from a percutaneous exposure ranges from 6% to 30% (5). OHSA requires employers to offer HBV vaccine to employees at risk of exposure.
Hepatitis C	3%–10% risk of transmission from an infected health care worker to a patient (22).

OTHER VIRAL INFECTIONS

○ HPV

- HPV appears in semen as cell free virus & epithelial cells
- Sperm wash reduce viral load
- Quadrivalent vaccine available (0,1-2,6months)

○ HTLV 1 and 2

- Ancient retro virus in humans, low potential to cause human disease
- HTLV 1: myelopathy (HAM) or T cell leukaemia
- HTLV 2: links to neurologic disorders suspected
- Sperm wash before insemination

○ HSV

- Sexual contact significant mode of transmission
- Avoid semen collection if lesion
- Infected male partner: Acyclovir / Valacyclovir to reduce viral shedding.
- Sperm wash: Effective.
- Women with HSV II: Acyclovir during pregnancy, LSCS.

○ CMV

- Semen donors screen before DI
- Risk of fetal & neonatal complications: primary infection in early pregnancy
- Sperm wash reduces risk



TAKE HOME MESSAGE

- Risk of transfer through ART is only when female is negative and male positive with virus present in semen
 - Risk reduction in DI can be done by screening infections in semen and quarantine it for window period
 - All semen samples from infected persons should be preserved in separate canisters after sperm wash
 - Density gradient with swim up leads to maximum infection reduction in sample
 - IVF and ICSI further reduces risk as virus is present as free virus or intracellular in semen
 - Only if prepared sample is free of virus by PCR for RNA and DNA no infection shall be transferred
- 