ASSISTED REPRODUCTION IN THE HIV-SERO DISCORDANT COUPLE

DR SALEEMA NOSARKA
REPRODUCTIVE MEDICINE SPECIALIST

DEPARTMENT OBSTETRICS & GYNAECOLOGY
STELLENBOSCH UNIVERSITY
INTRODUCTION

- 2014 HIV chronic but manageable disease
- HIV affects 60 million worldwide
- 86% reproductive age group 15-44 years
- HIV predominantly affects heterosexual couples
- 1/3 couples desire biological parenthood
INTRODUCTION

- Effective use of Highly Active Antiretroviral Therapy (HAART) → dramatic improvement in health & life expectancy for HIV-infected persons.
- Majority of HIV infections occur in sub-Saharan Africa.
- Current life expectancy is 30-40 years from diagnosis (Dx).
- Periconception pre-exposure prophylaxis (PrEP) reduces the risk of HIV transmission from an uninfected partner.
1990 CDC: recommended against reproductive assistance for HIV serodiscordant couples.

2002 ASRM revised guidelines: HIV serodiscordant couples may seek Rx.

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No. Pts = number of patients; Preg = clinical pregnancy rate (including miscarriage, ectopic, and normal pregnancy); Ong = ongoing, undelivered pregnancies; Infect = infections with HIV-1; *seven additional pregnancies occurred with the transfer of frozen embryos.

For complete references please visit: www.srmjournal.org.
2004 ESHRE ethics task force: ethically acceptable offer sperm washing & assisted reproduction HIV serodiscordant couples adequate precautions

2010 ASRM Ethics Committee guidelines: fertility clinics offer services HIV couples willing use risk - reduction therapies
2013 ASRM: guidelines reduce risk viral transmission

Basic principles include:
- ↓ viral load in infected partner
- ↓ non-infected partner’s exposure & infection risk
- discuss risk reduction strategies with couple
- always obtain informed consent
HIV/AIDS & HUMAN RIGHTS

- **2009** World Health Organisation (WHO) stated:
  “all couples and individuals have the right to decide freely & responsibly the number & spacing of their children & to have access to the information, education & means to do so” (including HIV infected couples)

- Need to integrate guiding principles into all aspects HIV Rx & care
HIV AND INFERTILITY

HIV + WOMAN

- Menstrual irregularities 20% - anovulation
- Prolonged amenorrhoea
- ↑ STI’s & PID’s - tubal factor infertility
- ↓ pregnancy rate (low CD4 count, HAART)
- ↓ ovarian reserve (↓ AMH & ↓ antral follicle count)
HIV AND INFERTILITY

HIV + MAN (HAART)

- hypogonadism
- testicular germ cell loss & atrophy
- ↓ sperm parameters
  - low sperm count
  - low sperm motility
  - abnormal sperm morphology
  - low sperm volume
ETHICAL ISSUES

- **2007** ACOG Ethics Committee stated:
  - ethical obligation provide ART to HIV serodiscordant & concordant couples

  - adhere basic principles ethics
    - **AUTONOMY** (pt. choice)
    - **BENEFICENCE** (dr promote health of pt.)
    - **NON-MALEFICENCE** (do no harm)
    - **JUSTICE**
ETHICAL CONCerns

1. Welfare of the offspring

2. Avoidance of seroconversion of uninfected partner in serodiscordant couple
WELFARE OF OFFSPRING

- RISK MOTHER-TO-CHILD TRANSMISSION
  - No intervention → risk 13-30%
  - HAART pregnancy & labour, elective c/section, no breastfeeding, ARV to neonate → risk vertical transmission < 2%
WELFARE OF OFFSPRING

➢ UNCERTAIN LONG-TERM PARENTAL PROGNOSIS

• Concern → best interest of child born to parents unavailable continuing childrearing

• Advances medical Rx HIV → ↑ life expectancy & quality of life

• 2014 ethically unjustifiable deny HIV couples Rx
FERTILITY Rx HIV-SERODISCORDANT COUPLE

- MULTI-DISCIPLINARY TEAM APPROACH
  - maternal-fetal medicine specialist
  - HIV/AIDS specialist
  - fertility specialist
  - neonatologist / paediatrician
  - psychiatrist / social worker / psychologist
FERTILITY Rx HIV-SERO DISCORDANT COUPLE

➢ INSTITUTION

- able treat pregnant HIV pt. & child
- adhere strict universal precautions
- separate laboratory facilities
- separate freezing facilities gametes & embryos
FERTILITY Rx HIV-SERODISCORDANT COUPLE

➢ PRE-CONCEPTUAL COUNSELLING

▪ Aims at discussing
  • reproductive options available & Rx failure
  • effect of HAART on reproductive function
  • risk of vertical transmission
  • factors affecting HIV transmission
  • long term health outcome & support networks
FERTILITY Rx HIV-SERO DISCORDANT COUPLE

PRE-CONCEPTUAL COUNSELLING

- Emphasize no Rx option 100% risk free
- Informed consent mandatory
- Preconceptual folic acid Rx
- Alternate options
  - HIV + man: adoption or use donor sperm
  - HIV + woman: surrogacy
FERTILITY Rx HIV-SERODISCORDANT COUPLE

- CLINICAL EVALUATION
  - HIV status couple
    - CD4 count, viral load
    - refer physician optimisation of HIV
  - HAART
    - commencement, compliance & resistance
  - Screen STI’s
    - syphilis, hepatitis, herpes, CMV
FERTILITY Rx HIV- SERODISCORDANT COUPLE

➤ Rate of HIV transmission 1 in 500-1000 acts unprotected intercourse
  • transfer man to woman 0.15%
  • transfer woman to man 0.09%

➤ Risk transmission increases
  • infected partner high viral load
  • uninfected partner genital infection or ulcers
FERTILITY Rx HIV-SERODISCORDANT COUPLE

➢ ROUTINE FERTILITY ASSESSMENT
  • semen analysis
  • assess ovulatory function & ovarian reserve
  • assess tubal patency (HSG or laparoscopy)
  • assess uterine cavity (hysteroscopy)
OPTIMAL ART Rx CANDIDATES

CRITERIA GUIDE SELECTING HIV PTS

- high motivation childbearing
- well-controlled HIV + stable CD4 count
- undetectable viral load (serum and semen)
- 90 % ARV medication adherence
TREATMENT OF HIV COUPLE

- 3 SCENARIOS HIV STATUS

1. FEMALE +, MALE –

2. FEMALE -, MALE +

3. FEMALE +, MALE +
Rx HIV DISCORDANT COUPLE

1. FEMALE +, MALE -

- Goal: prevent transmission to male partner & fetus
- Female partner ARV therapy
- Male partner PrEP option
- Pregnancy rates similar to HIV uninfected couples
Rx HIV DISCORDANT COUPLE

1. FEMALE +, MALE -

- No subfertility - **timed unprotected intercourse**
  - self insemination
  - Studies: seroconversion rate 0.01-0.41% per act
  - Rate ↑: partner ↑ viral load & genital ulcers

- Moderate male factor, unexplained infertility, anovulation ⇒ **IUI**

- Severe male factor, tubal factor, failed IUI ⇒ **IVF/ICSI**
Intrauterine Insemination (IUI)
Fertilisation; Invitro Fertilisation (IVF) and Intracytoplasmic Sperm Injection (ICSI)

Day 0

Day 1

Day 2

Day 3
Embryo Transfer

Day 2-3
Rx HIV DISCORDANT COUPLE

2. MALE +, FEMALE -

- goal prevent transmission female partner & fetus
- male partner ARV therapy
- female partner PrEP option
- sperm washing aims reduce risk transmission
Rx HIV DISCORDANT COUPLE

2. MALE +, FEMALE -

- Normal tubes, normal semen analysis
  ⇒ Sperm washing, IUI

- Tubal occlusion, severe male factor
  ⇒ Sperm washing, IVF/ICSI

- Donor sperm
HIV IN SEMEN

- Originally (1992) HIV present as free virus in seminal fluid & as cell-associated virus in non-spermatozoal cells

- Today HIV known not attach or infect sperm

- Sperm washing aims reduce risk transmission

- Goal washing “virus free” sperm - IUI / ICSI
HIV IN SEMEN

- Sperm washing prior to IUI eliminates round cells, seminal plasma & majority immotile sperm
- Sperm isolated by sequential density gradient & swim-up techniques
- Sperm tested by PCR assays presence HIV RNA
- Method 99.9% HIV sperm removal
STAGES OF SPERM PREPARATION

Semen

45-90% Density Gradient

HIV contaminated seminal plasma

Dead Sperm

Live Sperm

Fresh Medium

Live Sperm

Swim-up frozen

Aliquot taken for HIV testing
Systematic review of the effectiveness and safety of assisted reproduction techniques in couples serodiscordant for human immunodeficiency virus where the man is positive

Raquel Loja Vitorino, M.D., M.Sc., a Beatriz Gilda Grinsztejn, M.D., Ph.D., b Carlos Augusto Ferreira de Andrade, M.D., Ph.D., a Yara Hahr Marques Hökerberg, M.D., Ph.D., a Claudia Teresa Vieira de Souza, M.P.H., Ph.D., a Ruth Khalili Friedman, M.D., Ph.D., b and Sonia Regina Lambert Passos, M.D., Ph.D. a

Clinical Epidemiology Laboratory, and STD AIDS Clinical Research Laboratory, Evandro Chagas Clinical Research Institute (IPEC), Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil

Objective: To evaluate the effectiveness and safety of assisted reproduction techniques (ART) in human immunodeficiency virus (HIV) serodiscordant couples.

Design: Systematic review of five databases of noncomparative open intervention and observational studies of serodiscordant couples undergoing ART, with study selection and data extraction performed independently and in duplicate.

Setting: Tertiary fertility centers.

Patient(s): HIV serodiscordant couples where the man is HIV positive.

Intervention(s): Intruterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic injection (ICSI) performed after washed semen viral testing.

Main Outcome Measure(s): Pregnancy rates per cycle, cumulative pregnancy, abortion rate, and HIV seroconversion in newborns or women.

Result(s): Of the 658 abstracts retrieved, 41 were selected for review, and 17 full articles were included (3,900 IUI cycles in 1,184 couples in 11 aggregated studies and 738 ICSI/IVF cycles in 579 couples across 10 studies). The IUI and ICSI results were, respectively: pregnancy rates per cycle, 18% and 38.1%; cumulative pregnancy, 50% and 52.9%; and abortion rate, 15.6% and 20.6%. No seroconversions in women or newborns were detectable at birth or after 3 to 6 months.

Conclusion(s): Cumulative evidence suggests that ART is safe and effective for avoiding horizontal and vertical transmission in HIV serodiscordant couples. (Fertil Steril® 2011;95:1684–90. ©2011 by American Society for Reproductive Medicine.)

Key Words: Artificial insemination, assisted reproduction, HIV infection, infertility, intracytoplasmic sperm injection (ICSI), in vitro fertilization, reproductive techniques, systematic review
### TABLE 3

Effectiveness and safety in 11 studies of intrauterine insemination in serodiscordant couples with HIV.

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<th>Median age, men</th>
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### TABLE 4

Effectiveness and safety of intracytoplasmic sperm injection–in vitro fertilization in 10 studies of serodiscordant couples with HIV.

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ART SAFETY
- 11 studies - 3900 IUI cycles
- 10 studies - 738 IVF/ ICSI cycles
- no seroconversion women
- no infected newborns 6 month follow up

ART EFFECTIVENESS
- IUI median pregnancy rate/cycle 18%
- IVF/ICSI median pregnancy rate/cycle 38.6%
- IUI miscarriage rate 15.6%
- IVF/ICSI miscarriage rate 20.6%
REVIEW CONCLUSIONS

- ART safe & effective for avoiding horizontal & vertical transmission in HIV serodiscordant couples

- Patient profile important
  - good clinical status
  - undetectable viral load
  - high CD4 count
Rx HIV COUPLE

3. MALE +, FEMALE +

- ESHRE advises against → orphaned child
- Assess general health & wellbeing couple
- Test CD4 count, viral load, use of HAART
- Timed natural conception option - risks
- Sperm washing & ART preferred option
CONCLUSIONS

- 2014 HIV serious manageable chronic disease

- **Demand** for risk-reduction fertility Rx in HIV discordant couples rapidly rising

- Current HIV treatments limit risk of viral transmission to partner & offspring

- Appropriate **safe interventions** possible
CONCLUSIONS

- PrEP reduce transmission risk during intercourse
- Sperm washing & IUI / ICSI → HIV + male
- HAART & elective Caesarean section decrease vertical transmission rate 2% → HIV + female
- 2014 fertility clinics offer services HIV couples
THANK YOU!!