

CONCEPTION IN HIV-DISCORDANT COUPLES

Second Edition

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Conception in HIV-Discordant Couples

J. T. Wilde

Introduction

Highly active antiretroviral therapy (HAART) has greatly improved the quality of life of patients infected with human immunodeficiency virus (HIV). Furthermore, the combination of well-being and improved life expectancy has prompted a number of HIV-discordant couples, where the male is HIV-positive and the female negative, or vice versa, to consider starting a family. This situation is especially relevant to HIV-infected hemophilic men and their partners. Unprotected sexual intercourse is the main way in which HIV is transmitted and therefore it is essential to develop strategies which minimize the risk of HIV-negative females becoming infected by semen as they are trying to conceive. This monograph discusses the relative merits of the alternative methods of conception that are available to these couples.

Risk of Sexual Transmission of HIV

Semen contains the male reproductive cell, the spermatozoa, and other cells including macrophages, lymphocytes, and neutrophils suspended in a fluid, the seminal plasma. HIV has been found to be present in the non-spermatozoa cells and as free virus in the seminal plasma [1]. The spermatozoa can also be infected with HIV, but whether the virus remains alive in these cells and therefore contributes to sexual transmission has still to be clarified [2-4]. As the spermatozoa contribute only around 10% of the total volume of semen, even if these cells contain active HIV they contribute only a small part to the overall "risk" of sexual transmission by semen.

Studies of the risk of HIV transmission through unprotected intercourse either pre-date HAART or have been performed in populations to whom HAART has not been available. It has been estimated that the female partner of an HIV-positive man has a 0.1 to 0.2% risk of becoming infected with HIV as a consequence of a single act of unprotected intercourse [5]. In a further

study, the risk of HIV transmission through sexual intercourse from an HIV-positive male to an HIV-negative female was estimated as being around 1 in 10 for less than 10 unprotected contacts and around 1 in 4 after 2,000 contacts [6]. Although, as would be expected, this study reports a higher risk of HIV transmission with increasing unprotected contacts, the actual risk of infection in individual couples was quite variable. Risk variability can be explained by a number of factors such as the total number of HIV viral particles in the blood of the infected male, the presence of co-existing sexual infection in either partner (both discussed further below), and individual susceptibility to HIV infection.

In a study of 198 female sexual partners of HIV-infected hemophilic German men carried out in the mid-1980s prior to the introduction of widespread safe sexual practice, a 10% transmission rate of HIV was reported [7].

Three studies report on the risk of HIV acquisition in couples attempting conception by unprotected intercourse at ovulation with protected intercourse using condoms at other times. In a prospective observational study of 92 HIV-discordant couples (males HIV-positive), 4 females seroconverted, 2 in the third trimester of pregnancy and 2 in the period following delivery [8]. It has been suggested that, in this study, advice concerning safe sexual practice was disregarded in some couples once the female had become pregnant.

The other two studies also assessed the risk of HIV transmission from HIV-positive hemophilic men to their female partners. In both these studies the couples were counselled and advised to have sexual intercourse only around the time of ovulation, as indicated by the use of an ovulation detection urine testing kit. In the first report from Cardiff, U.K., 26 children were born to 18 discordant couples over a 15-year period and none of the female partners contracted HIV [9]. In the other study from the Royal Free Hospital, London, U.K., out of 14 couples with a

total of 19 children between them, 1 female partner was found to be HIV positive [10]. None of the children became infected.

Overall, it would appear that unprotected sex for the purposes of conception in couples with the HIV-infected man not taking HAART carries a risk of HIV transmission to the female of no more than 8%.

Effect of quantity of HIV in blood / semen on transmission risk

The number of individual viral particles (viral load) in the blood is highly correlated with transmission risk. In a study of 415 Ugandan couples in which one partner was HIV-positive and the other HIV-negative, the viral load of the infected partner was the most powerful predictor of HIV transmission [11]. This observation is likely to be due to the fact that blood viral load correlates closely with semen viral load. Usually, HIV-infected men have HIV levels in semen around 10 times lower than the viral load in the blood [12]. However, a small number of males have HIV levels in semen that exceed blood levels [13]. These so-called “super shedders” may impart a higher than anticipated risk of HIV transmission to their partners.

Effective HAART is associated with a marked reduction in HIV load in semen [14]. As a consequence, it is probable that the risk of sexual transmission of HIV is lower in individuals on HAART with undetectable blood viral loads (i.e., less than 50 copies of the virus per mL of blood) compared with individuals who do not fully suppress circulating virus. However, this is not proven. HIV can still be detected in the semen of men on HAART with no detectable virus in the blood, imparting a risk of HIV transmission during intercourse [15, 16].

Concurrent sexually transmitted infection (STI) and HIV transmission risk

Any damage to the protective lining of the female genital tract increases the risk of HIV particles, if present in semen, passing into the bloodstream and infecting the individual. Damage can occur as a result of trauma during intercourse or from pre-existing infection of the genital tract by bacteria, trichomonas, or viruses

such as herpes simplex. Also, the presence of a genital tract infection in the male partner is associated with an increase in the HIV load in semen, presumably due to passage of the virus from the blood into the genital tract at sites where the lining has been damaged from the infection. The increased semen viral load will increase the risk of HIV transmission [12].

Effects of Antiviral Agents on Semen Quality

The long-term effects of current HAART medications on the production of sperm and on sperm quality are unclear as ongoing studies looking at these issues have yet to report. Although zidovudine (AZT) has been reported to improve sperm counts, it and other drugs of the same type have been shown to be incorporated into the DNA of an individual’s cells and are therefore likely to become contained in sperm DNA with as yet unknown consequences for the future development of the fetus should conception occur.

Conception Methods for HIV-Discordant Couples

HIV-discordant couples who wish to have a child need to balance the chances of conception against the risk of HIV transmission to the mother, and possibly subsequently to the child. In order to make an appropriate decision with regard to their preferred method of conception, couples require detailed information and thorough counselling about the alternatives available and the associated risk of viral transmission. The fundamental principle behind any conception method is to minimize the risk of HIV transmission whilst optimizing the chance of conception [17].

The alternative conception methods available for HIV-discordant couples are as follows:

- **Timed ovulatory intercourse:** Unprotected sexual intercourse is restricted to the time of ovulation (discussed in detail below).
- **Artificial insemination of the female with washed sperm from her HIV-positive partner:** This method involves direct

injection of the sperm into the uterus after the sperm has been “washed” to remove seminal plasma and non-spermatozoal cells (discussed in detail below).

- ***In vitro* fertilization (IVF) with prepared sperm from the HIV-positive partner:** This method involves the removal of sperm from the seminal plasma and the collection of eggs from the female by a surgical procedure such as laparoscopy. The eggs are then fertilized in a test tube (*in vitro* fertilization). IVF is routinely indicated in couples with fertility problems and has been considered as an alternative to artificial insemination of the female with washed semen in discordant couples to further reduce the risk of HIV transmission. However, because of the invasive nature and costs of this procedure, it is usually restricted to HIV-discordant couples who have co-existing infertility problems.
- **Artificial insemination of the female with sperm from an HIV-negative male donor:** This method totally eliminates the risk of HIV transmission to the female but is not acceptable to many couples.

Pre-conception assessment

Couples who decide to proceed with either timed ovulatory intercourse or artificial insemination with washed sperm should undergo fertility assessment in a specialist unit beforehand. This is to ensure that pregnancy is possible. Both the male and female should also undergo genital tract infection screening so that any existing infection can be treated, therefore reducing the risk of HIV transmission.

Fertility assessment

Semen analysis is performed on the male. The semen analysis should be “normal” according to the World Health Organization criteria [18]. In brief, the minimum criteria are a sperm count greater than 20 million cells per mL with greater than 50% of the sperm being mobile. Patients with borderline sperm quality may still attempt timed ovulatory intercourse but they will need specialist advice on the chances of conception. If more serious sperm abnormalities are present, IVF can be considered.

Female partners must have open fallopian tubes and a normal uterine cavity. These can be assessed by either a special X-ray test called a hysterosalpingogram or laparoscopy combined with hysteroscopy (direct inspection of the cavity of the uterus by a scope passed up the vagina and through the cervix).

Next, normal ovulation has to be demonstrated. If a woman is ovulating normally, she will have regular menstrual cycles. Ovulation is confirmed by the finding of a normal level of the hormone progesterone mid-way through the second half of the menstrual cycle (the luteal phase). Irregular cycles indicate absence of ovulation and the cause of this must be determined. Treatment will depend upon the cause. If ovulation can be induced by drugs such as clomiphene citrate (confirmed by normal mid-luteal phase progesterone levels) then attempts at conception can proceed.

Infection screening

It is recommended that both male and female partners undergo a thorough sexual health examination and screening for concurrent sexually transmitted infection (STI). This should be performed on the female before fertility investigations, as cervical manipulation during a hysterosalpingogram in the presence of infection carries an increased risk of pelvic inflammatory disease and subsequent damage to the fallopian tubes. Treatment of existing STI in the male has been shown to significantly reduce the HIV load in semen [19]. Therefore, if infection is detected, it should be eradicated before conception is attempted.

Female partners should have an HIV test performed to ensure that they are not infected. They should also have their blood tested to check whether or not they are immune to the rubella virus, the virus that causes German measles. If the female is not immune, rubella immunization should be offered in order to protect her from catching German measles during pregnancy. If either partner has a history of genital herpes, ideally both should be taking appropriate anti-viral medication at the time of unprotected intercourse to prevent infection spread to the uninfected partner.

General pre-pregnancy preparation

If a decision is made to proceed with conception, routine pre-pregnancy measures should be initiated. These include the female taking folic acid (0.4mg/day) three months prior to the planned conception date and continuing until at least the 12th week of pregnancy. The female should also be up to date with her cervical screening.

Timed ovulatory intercourse

Using this method, the risk of HIV transmission is the same as that of unprotected sexual intercourse. However, this method probably offers the best chance of conception and is arguably the only reasonable alternative (provided all possible measures have been taken to minimize transmission risk) when other methods are not available or not acceptable. It should not be advised if alternative forms of safer conception are available.

Before attempting this method of conception, it is recommended that the fertility of each partner be confirmed with the appropriate tests and that any genital infection found in either partner be appropriately treated. Semen viral load should be checked regardless of whether or not the man is on HAART. Even if HIV is not detected in the semen or the viral load is low, it should ideally be checked on one or two further occasions to exclude the possibility that he is a "super shedder." Men on HAART with undetectable HIV in their blood and semen should not be considered totally risk free. However, while there have been no studies performed to assess transmission risk in this situation, it is likely to be very low, making timed ovulatory intercourse a relatively safe option in this population.

Artificial insemination with washed sperm

Sperm washing involves centrifugation of semen, with subsequent removal of seminal plasma and non-seminal cells and resuspension of sperm in a sterile fluid. This process greatly minimizes the risk of HIV transmission to the female and at present is considered by many clinicians to be the preferred conception method for HIV-discordant couples.

Professor AE Semprini of Milan, Italy, pioneered the clinical application of sperm washing and has been offering assisted conception to HIV-discordant couples using this technique since 1989 [20]. Since then, a number of groups have demonstrated the effectiveness of this procedure in reducing the amount of transmissible HIV in semen [23, 24]. In a study performed at the Chelsea and Westminster Hospital, 10 of 11 HIV-infected men were found to have HIV in their semen. Following sperm washing and using a very sensitive detection technique, HIV was no longer present in any of the sperm samples that were positive before washing [25].

Unfortunately, sperm washing conception services are very expensive to set up and run, and therefore very few other centres have so far been established worldwide. Centres offering a sperm washing conception service at the present time include the Chelsea and Westminster Hospital in London, U.K.; Munich, Germany; and Barcelona, Spain. As of early 2001, over 3,000 cycles of sperm washing and intrauterine insemination or *in vitro* fertilization have been performed in these centres. The pregnancy rate has been 12%, with over 300 live births and no reported transmission of HIV to any of the female partners or children [21, 22].

Usually couples will have to pay to enter a sperm washing conception program, as it is exceptional for funding to be obtained from other sources. In the U.K., for example, couples are not routinely funded by the National Health Service. The cost of sperm washing conception may be prohibitive for many couples; in the U.K. the present cost of the procedure is around £1,500.

Once the pre-screening tests and counselling are completed, a timetable for the procedure is agreed upon. Insemination of the washed sperm can be performed during a natural menstrual cycle. Twenty-four hours after ovulation has occurred (and been confirmed using a kit that detects hormone level changes in the urine), the male partner is invited to donate semen by masturbation. The semen is collected into a sterile container and "washed." A sample of washed sperm is taken and screened for the presence of HIV. If the test is negative, the

sperm is inseminated into the female using a soft catheter inserted through the cervix into the uterus. If rapid HIV testing of washed sperm is not available, semen can be collected from the male at any time, washed and frozen pending the HIV test result. If the test is negative, the sperm can be thawed and inseminated into the female at the time of a future ovulation. Freezing and thawing of sperm does not result in a significant reduction in the chance of conception.

If there has been a failure of conception with natural cycle insemination or if the female has a fertility problem, then insemination with washed sperm can be tried following hormonal stimulation of ovulation. There is a risk, however, of multiple births in 10% of pregnancies with this treatment.

A pregnancy test is performed two weeks after insemination and if it is positive the female is closely screened for HIV throughout the rest of the pregnancy. Based on presently available data, the chance of pregnancy using this technique is about 10%. Several attempts may therefore have to be performed.

Although it is now considered routine to test washed sperm for HIV prior to insemination, the technique used is very expensive and contributes significantly to the high cost of sperm washing services. However, as large numbers of couples were safely treated by Semprini prior to the introduction of post-wash HIV testing, it would appear that the washing technique is fully effective at removing living virus. Therefore, a strong case could be made for omitting post-wash testing, which reduces the cost of the procedure considerably.

Conclusion

Male positive/female negative HIV-discordant couples wishing to have children should be offered appropriate counselling and advice before attempting conception. They should make a decision as to which option to choose based on balancing the chances of conception against risk of HIV transmission. Of the two main alternatives, artificial insemination with

washed sperm is the safer option, although the conception rate for each attempt is about 10%. However, this service is not widely available and is very expensive. If sperm washing conception is not feasible or acceptable, couples can consider timed ovulatory intercourse which, although not completely without risk, may be considered a risk worth taking because of the higher chance of conception.

The costs of an unnecessarily HIV-infected adult or child are considerable in human and economic terms. Therefore, it is crucial that appropriate, effective strategies are developed to protect transmission of HIV in discordant couples who are wishing to conceive.

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