

Fertility Options for HIV Discordant Couples



**Southern Ontario
Fertility Technologies**

Introduction

The use of highly active antiretroviral therapy has modified the prognosis of HIV infection. As a result, many couples in which one of the partners is HIV positive have a strong desire for children. At the S.O.F.T. clinic, we have been involved with a number of couples in which the male is HIV positive and the female is not.

Intercourse and HIV

Protected intercourse is strongly recommended for serodifferent couples as transmission of HIV from one partner to the other is thought to occur approximately in every 100-200 sexual encounters. Although treatment of HIV and attaining low viral loads and good CD4 counts probably decreases the risk of transmission, it still can occur.

There is fairly good evidence that the viral load in blood is not always correlated to the viral load in the semen. All of the factors determining the viral load in the semen are not known but inflammation in either the urinary tract or the genital tract (I.E. – a bladder infection or prostatitis) could increase the viral load in the semen.

Factors specific to intercourse or the female partner could also determine the chance of transmission. It is commonly believed that individuals differ in their susceptibility to HIV. Intercourse technique and the amount of micro-trauma to the female at the time of intercourse could also affect the chance of transmission.

Assisted Reproductive Technologies (ART) and HIV

Many HIV-serodifferent couples are seeking ART to decrease the risk of HIV sexual transmission. This could take place in two different circumstances. Either the woman or the man could be HIV positive.

In the first circumstances (the **HIV positive woman**), the man's sperm sample could be collected, possibly processed, and used in some form of ART or just used for self insemination. The S.O.F.T. clinic has had no experience in this situation. The chance of "vertical" transmission from the mother to the unborn baby would always exist. Good evidence exists that this transmission can be drastically reduced by adequate HIV treatment but the risk always remains.

The second situation (the **HIV positive male**) is the circumstance that this information sheet will address. As far as we know, if HIV transmission does not occur from the male to the female, the child will be unaffected. There is a theoretical possibility of transmission from the male to the baby. If the sperm cell that penetrated the egg was HIV infected, the fetus could be HIV positive without the mother being infected. This is unlikely as we believe that sperm cells are not infected by the HIV virus. However, some controversy exists with the last statement. Early publications reported HIV DNA by polymerase chain reaction in situ hybridization (a technique that can detect the location, through the microscope, of very, very small amounts of virus) in sperm. The presence of HIV in sperm has not been confirmed by recent studies. Most experts believe sperm lack the CD4 and CCR5 receptors on their surface that allow the virus to

bind with and enter the cell. HIV is probably found in highest concentration in the white cells present in the semen. Some may occur free in the liquid but none should be inside the sperm.

Technologies Available

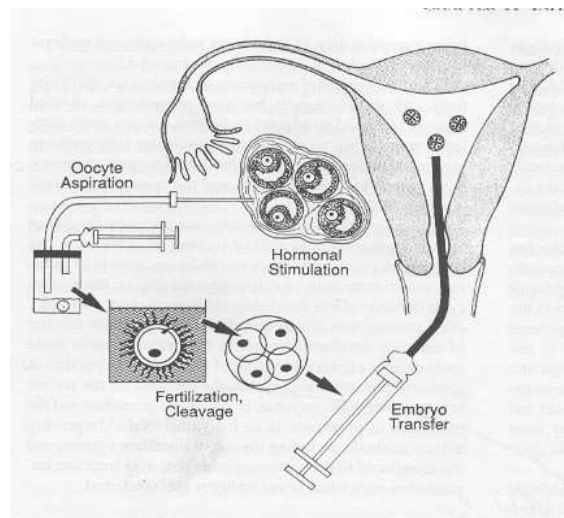
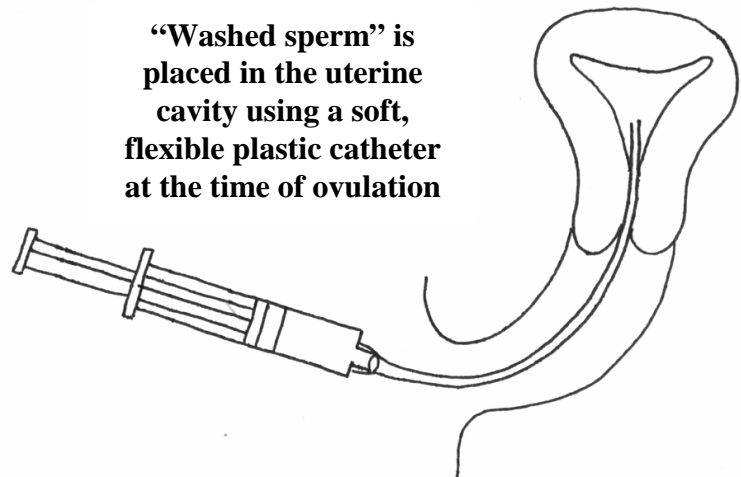
Several Assisted Reproductive Technologies potentially could be used to reduce or eliminate the possibility of transmission of AIDS from the HIV infected male to the non-HIV infected female.

The only technology that eliminates the risk of transmission is **donor insemination**. This technology has been traditionally available for these couples and currently available through most institutional and private infertility clinics in Canada. Donor insemination usually involves monitoring of the female's cycle, usually with blood tests and vaginal ultrasound and intrauterine insemination of "washed" donor sperm at the time of ovulation. Donor insemination done through fertility clinics usually uses frozen, anonymous donor sperm, purchased from a commercial sperm bank. This technology is covered in detail in a separate information sheet. Other possibilities exist (known donor, self insemination). Donor insemination has the advantage of complete risk elimination but the disadvantage of loss of the genetic contribution to the baby of the male.

Considerable evidence exists that **intrauterine insemination** of HIV-negative women with "washed" semen obtained from HIV infected men is a reasonable risk reduction procedure. It is this technology that the information sheet will address in detail. The S.O.F.T. clinic does not specialize in the procedure for this circumstance. However, we feel that with detailed

informed consent (outlining of the pros and cons); the couple should not be denied this technology. Unfortunately, as far as we know this is not available in other clinics in Canada.

The other potential technology for couples in this circumstance is **In Vitro Fertilization (IVF)**. S.O.F.T. has an information sheet available on IVF. The published literature on this technology all also includes **Intracytoplasmic Sperm Injection (ICSI)**. IVF involves the stimulation of the female's cycle to produce many (10-20) eggs. The cycle is monitored using blood tests and vaginal ultrasound and when the eggs are mature; they are retrieved from the body. The eggs are then fertilized outside of the body. In traditional IVF, fertilization is done by placing the sperm with the eggs and incubating them. ICSI involves isolating one egg and sperm



at a time. The egg is held and a single sperm is injected into it.

ICSI is usually done to overcome severe male factor infertility and more information on it can be found in the information sheet on ICSI or on Male Infertility. ICSI has been used in HIV-discordant couples because theoretically by using only a single sperm, the chance of HIV DNA being introduced into the female genital tract should be reduced. This may not be entirely true as HIV virus is believed to be present in the semen as free particles in the seminal plasma (fluid without the cells) and as cell-associated provirus in the CD4-carrying non-sperm cells (white cells or puss cells are found in the semen).

Diagram outlining the IVF process



With ICSI a Single Sperm is Injected into the Egg

Although a white cell would not be injected into the egg during the ICSI procedure, some seminal plasma is.

A study has been reported in which 68 HIV discordant couples underwent IVF and ICSI with no seroconversion. The advantage of this procedure is the high pregnancy rate per cycle which would decrease the couples need to submit to the cumulative risk of many cycles. The

disadvantages of IVF and ICSI are that it is not to my knowledge available in Canada for HIV discordant couples; it is expensive and invasive technology for a couple who may not have any fertility problems to overcome.

Intrauterine insemination

Intrauterine insemination is an Assisted Reproductive Technology which is widely used for mild to moderate infertility after simple ovulation induction (giving pills to cause production of more eggs) has failed or if mild male factor infertility exists. It involves monitoring of the woman's cycle with blood tests and ultrasounds. Sometimes medications are used to promote ovulation or produce more eggs. When the eggs are mature and about to be released, washed sperm is placed into the uterus with a soft, pliable catheter. More information on intrauterine insemination is available on the many information sheets available on this subject.

Interest in intrauterine insemination with washed sperm as a risk reduction procedure for couples where the male is HIV positive and the female is not has increased due to a number of publications in the literature that indicate this can cause considerable risk reduction while allowing the couple to have their own biological child. However, any couple considering this must realize that this is a risk reduction procedure and does not eliminate the risk.

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Balancing The Risk And Benefits

In this section, I will attempt to present the current scientific evidence concerning sperm preparation and intrauterine insemination as a risk reduction procedure so that you may make an informed decision about this technology. The S.O.F.T. Clinic does not specialize in this procedure. When the clinic was founded in Oct. 2000, a considerable body of evidence existed in favour of sperm washing for HIV discordant couples and it was being done in other countries. At that time, both the Canadian and American Fertility Associations did not advise it. Since then, more evidence has accumulated and the American Society of Reproductive Medicine has stated it is a technology that is reasonable if the couple has been given informed consent.

Because S.O.F.T. does not specialize in HIV, **we like your HIV doctor to be involved.** Your HIV doctor should make sure that the HIV is optimally treated; be aware you are considering infertility technologies; and be available to follow the woman to detect any seroconversion and treat the HIV should it occur.

Viral Loads In Blood, Semen and Sperm Preparations

Viral loads are usually determined using a technology called **Polymerase Chain Reaction (PCR)**. This is a method that is able to detect minute quantities because it multiplies them in order to measure them. PCR can be done by several different methods and each has a **specific detection threshold**. Detection thresholds for PCR vary from 20 to 340 copies / ml. This means if a sample tests negative for HIV, HIV DNA or RNA could still be present in the sample. In fact, finding a negative by PCR could mean that there are no viral particles or there could be 19 / ml in the case of the most sensitive test or there could be over 300 with the least sensitive test.

This helps to explain that different studies in the literature have found different percentages of prepared semen with viral particles present. Using sensitive PCR testing, HIV particles will be found in the blood of about 40%, in the seminal plasma of 30-40%, and in the washed sperm preparation of about 5-10%. These figures are my impression of the averages from the literature available.

Whether PCR testing of the washed samples and discarding of the positive samples improves the chance of non-transmission is controversial and has never been proven. Same day HIV testing of processed semen is very difficult and extremely expensive for any lab to provide. Some studies in the literature have done PCR testing but frozen the sperm preparations to be thawed and used at a later time. Several series have been done without PCR testing. **PCR testing of the washed samples is not available at S.O.F.T.**

Whether sperm are present in the washed preparation cannot be predicted but probably depends on many factors.

HIV particles are less likely to be present in the preparation if the blood viral load is low and the CD4 count is good. Ideally, at S.O.F.T. we would like to see an undetectable viral load and a CD4 count of over 300.

HIV particles may be less likely to be present in the sperm preparation when antiretroviral therapy is currently being used and may be less likely the longer it is used. Although it is not proven, we encourage the male partner to be on at least minimal antiretroviral therapy during these procedures even if the viral loads and CD4 counts are excellent.

HIV particles are more likely to be present in the prepared sperm if some form of inflammation is present in the male's urinary or genital tract. Therefore, attempts at this technology should be remote from any urinary tract infections (bladder infections) or prostatitis.

S.O.F.T. does not specialize in Reproductive Technologies for HIV serodiscordant couples. However, we feel that because the current medical literature indicates that sperm washing and intrauterine insemination is a very reasonable risk reduction procedure for these couples and presents no risk to our other infertility couples, that we are ethically obliged to offer it to our patients.

No specific protocol for sperm washing appears to be more effective at removing the viral particles. Theoretically, the more sperm washing repeats that are done, the better the chance of removing more viral particles. However, practically there is a limit to this as the % of sperm recovered decreases with each sperm washing step. At S.O.F.T. a minimum of two steps (the same as described in most of the clinical trials) are done. Additional steps may be added if the original sperm count will allow it.

Although no evidence exists, it makes sense that trauma or inflammation of the female genital tract may affect the likelihood of transmission. Therefore, the insemination procedure will not be completed if there is any indication of a vaginal infection. Occasionally, the catheter used for insemination causes bleeding because it damages a small blood vessel in the cervical canal. This is usually of no consequences, but if it occurs during the procedure in a HIV discordant couple, the procedure will be halted.

The Clinical Evidence

In Italy and Spain insemination of HIV-negative women with processed semen obtained from HIV-positive men has been performed since 1992. **Over 5,000 inseminations have been done without a documented transmission.** Two large series have also been reported with 350 and 60 couples with no seroconversions. A program also exists in Boston, USA in which no conversions have been documented.

Preparation

Even though the HIV discordant couple usually does not have infertility, a basic infertility investigation is done before beginning treatment. This includes a complete history and appropriate directed physical examination. It also includes blood testing on the third day of the woman's cycle to determine if any hormonal problems exist and a hysterosalpingogram (tubal dye test) to determine that the uterine cavity is normal and the tubes are open.

The HIV positive male must also do a semen analysis. There is no information in the literature on the effect of HIV on sperm counts but we have found two HIV positive males with no sperm. One other had a low sperm count due to the use of androgen supplementation. This recovered when it was stopped.

Both members of the couple will have "program blood work" done just as all couples having intrauterine insemination.

We also request copies of the male's most recent CD4 count and viral load. In an ideal world we would do PCR testing on the sperm sample to see if any virus was present. Unfortunately, we are not equipped to do this and the couple must understand this before submitting to the procedure. Remember, that the literature does not support PCR testing of the sperm samples but it is done in some clinics.

If no abnormalities are found, treatment is usually started with spontaneous (no medication) cycles. An information sheet is available on this and other intrauterine insemination protocols.

Results

S.O.F.T. does not specialize in HIV and so our numbers are very small. Our small case series was presented at the 2006 meeting of the Canadian Fertility and Andrology Society. Obviously, this is a very small series and does little to add to our scientific knowledge. The purpose of the presentation was more to make the point that all fertility clinics should provide this service. An abstract of that presentation is included here for your interest.

To the best of our knowledge, Our four IUI pregnancies are the first and, up until now, the only pregnancies produced in Canada using Artificial Reproductive Technologies (other than Donor Insemination) For HIV serodiscordant couples.

Canada's first ten pregnancies for HIV discordant couples produced by sperm washing and intrauterine insemination

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Objective: To document this small case series of HIV discordant couples.

Methods: Sperm washing and intrauterine insemination has been offered in our clinic since 2001. Pregnancies occurring from this procedure have been documented and compiled and are presented here. All couples were screened by day three blood work (FSH, LH, TSH, prolactin and estradiol), hysterosalpingogram, and semen analysis. HIV conversion was followed by HIV testing for the female in each trimester and postpartum.

Results: Eleven pregnancies occurred in 10 couples. One couple returned for a second pregnancy. Infertility factors were found in 4 of the couples. Two had semen analysis which were lower than WHO criteria, one had PCOS diagnosed by using the criteria established by the Modified Consensus of the National Institute of Child Health and Human Development in 1990 and modified (2004) at an international consensus, and one couple had low sperm count and PCOS. Female age ranged from 22 to 39 (mean 31.8). Two couples had one previous child. Twenty eight inseminations were done for a pregnancy rate of $(11/28 = 39.3\%)$. Twenty inseminations were done with spontaneous cycles, 5 with clomiphene citrate, one with clomiphene citrate and injectable fertility medications and two with letrozole. One positive pregnancy occurred which ended in spontaneous abortion. No seroconversions occurred. Eight of these babies have been delivered and no congenital abnormalities have been reported.

Conclusions: Most fertility organizations have recognized sperm washing and intrauterine insemination as a reasonable risk reduction procedure for HIV discordant couples. However, fertility clinics have been slow to offer this program. Hopefully, this small case series will be reassuring as it demonstrates no seroconversions and a very acceptable pregnancy rate.

We have also done monitoring and arranged retrieval, ICSI and transfer in Chicago for one couple who are currently pregnant with twins after their first attempt.

My impression is that if no infertility problems are apparent in the couple, they become pregnant at a higher rate than the corresponding infertility couples using the same technology.

No seroconversions have occurred. Our request for our couples who are considering this technology is that they undergo HIV testing in each trimester and that the baby be tested at birth and at 6 months.

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Check out our web page at **www.soft-infertility.com**