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[Intervention Review]

Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples

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ABSTRACT

Background

Sperm washing is a term used to describe the process in which individual spermatozoa are separated from the seminal fluid. Sperm washing is used to prevent HIV transmission but allow conception in sero-discordant couples, where the male is HIV positive, but the female is HIV negative. This procedure is based on the observation that HIV cannot attach itself to spermatozoa, but it can be found in the fluid and cells surrounding spermatozoa.

Objectives

To determine the benefits and harms of sperm washing of HIV-infected males when used to prevent the transmission of HIV but allowing conception in the HIV-negative female.

Search methods

We searched the Cochrane HIV/AIDS Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, SCOPUS, AIDsearch, AJOL, LILACS and INDEX MEDICUS. We also searched the following conference proceedings for relevant abstracts:The International AIDS Conference; The Conference on Retroviruses and Opportunistic Infections (CROI); The British HIV Association (BHIVA) Conference; The International Conference of Obstetricians and Gynecologists (FIGO); The American Academy of HIV Medicine Conference; The Australasian HIV/AIDS Conference; The American Society for Reproductive Medicine (ASRM) conferences and website; The European Society for Human Reproduction and Embryology (ESHRE) conferences and websites, and the British Fertility Society (BFS) conferences and website. We also conducted a search of the website: www.ClinicalTrials.gov. The date of the most recent Cochrane HIV/AIDS Group Controlled Trials Register search was on the 10th of November, 2010.

Selection criteria

We preferentially looked for randomised or quasi-randomised controlled trials on sperm washing, aimed at preventing HIV transmission from HIV-infected men but allowing conception in sero-discordant couples, irrespective of publication status, year of publication, or language in the review.

Data collection and analysis

No relevant trials were identified for inclusion in this review.

Main results

Forty-four studies were identified, but none of them were suitable for inclusion in this review.

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Authors' conclusions

Reports on the use of sperm washing to prevent HIV transmission, from HIV-infected men but allowing conception in sero-discordant couples, are currently limited to observational studies. No randomised controlled trial has assessed the benefit or risk of sperm washing to prevent HIV transmission from HIV-infected men but allow conception in sero-discordant couples. Thus, this systematic review identifies the need for a multicentre randomised controlled trial assessing the benefits and possible risks of sperm washing in preventing HIV transmission from HIV-infected men but allow conception in sero-discordant couples.

PLAIN LANGUAGE SUMMARY

Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples

Sperm washing is a technique that concentrates and separates the seminal fluid from the sperm in HIV-positive males. HIV is known to reside in the semen of HIV-positive men. When a woman wants to get pregnant, she is artificially inseminated with the sperm after it is washed and becomes virus-free. Sperm washing is done with the help of a centrifuge. The centrifuge is a device that spins at a high speed to separate the sperm from the seminal fluid in a given sample of semen. The sperm is then purified in a solution twice, in order to clean other unwanted substances in it, including the HIV. This technique was first introduced in 1992 in Milan, Italy by Augusto Enrico Semprini and colleagues, with the aim of helping HIV positive couples to conceive a healthy baby and to ensure that females do not acquire the disease from an HIV-positive male. Nowadays, many couples opt for sperm washing because it prevents the female partner from getting infected with HIV and enables the HIV positive male to propagate a healthy family. However, this process can be very lengthy and expensive. It is very helpful if both partners understand sperm washing to be a risk-reduction method and not a risk-free method as, technically, the virus could still be present in the washed sample at a titer below the detection limit of the HIV assay. There have been no reports of seroconversion in the female partner when semen has been correctly processed. Hence, the risks of not performing sperm washing need to be strongly discussed with sero-discordant couples.

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BACKGROUND

The initiation and advancement of highly active antiretroviral therapy (HAART) in the past decade has transformed the lives of HIV infected men and women and has led to the redefinition of the HIV infection as a chronic disease (Scandlyn 2000). Sperm washing and assisted reproduction technologies have been proposed for HIV-discordant couples in order to minimize the chances of HIV transmission during conception attempts (Semprini 2004). Alternative options such as donor insemination or child adoption were also suggested to allow conception in these couples. However, the remarkable changes in the management and prognosis of HIV infection have shown that it is very possible to prevent HIV transmission, yet allow conception, in HIV sero-discordant couples.

Description of the condition

Sperm washing is used to prevent HIV transmission but allow conception in sero-discordant couples, where the male is HIV-positive, but the female is HIV-negative. In this situation, the major concern lies in the risk of male-to-female HIV sexual transmission. For many years, donor sperm insemination was the only alternative to achieve a safe pregnancy in this situation. However, this option is not well accepted by many HIV-discordant couples, whose desire is to bear their own children (Ohl 2003). In Italy for example, donor sperm insemination is no longer a viable reproductive option for sero-discordant couples (Robertson 2004), probably because of the success of the sperm washing program in Italy. There was great interest when sperm washing was first reported in 1992. Since then, much work has been done in the area of sperm washing. In Europe, there are centres involved in sperm-washing programmes - Centres for Reproductive Assisted Techniques for HIV in Europe (CREAThE network), whose primary objective has been to pool knowledge, experience, and results in order to improve the service offered to HIV-sero-discordant couples (Bujan 2007). The study was the first multi-centre study of the use of sperm washing in couples in which the male partner was infected and the couple wished to conceive. It is the largest series published to date to confirm the safety and efficacy of assisted reproduction, where sperm washing was used as the primary means of avoiding HIV infection in the female partner.

Semen processing techniques used in assisted reproduction have been modified for use in separating spermatozoa from infectious elements in semen. The final objective of these “sperm washing” techniques is to obtain a spermatozoa free from DNA and RNA HIV. After the sperm-washing procedure, there are three main options to achieve a pregnancy: intrauterine insemination (IUI), in vitro fertilisation (IVF). and intracytoplasmic sperm injection (ICSI) (Riley 2005).

There is wide experience with intrauterine insemination (IUI) and in vitro fertilisation (IVF) in HIV-sero-discordant couples in Europe and the United Kingdom (Riley 2005), while Intracytoplasmic Sperm Injection (ICSI) is the only recommended option in some regions, like the United States of America. Semprini, et al. have the largest experience with HIV-negative women undergoing IUI with sperm concentrates from HIV-infected male partners (Semprini 2004). No cases of horizontal HIV transmission were recorded after more than 4500 inseminations (Vernazza 2006). Similar experiences have been reported by others (Bujan 2004) (Marina 1998). Likewise, no seroconversion events have been recorded in women who have undergone IVF (Sauer 2002) or ICSI (Ohl 2003) in recent years. The pregnancy rate per procedure after sperm washing ranges from 15 to 30% for IUI and from 22 to 45% for IVF (Karon 2001). More studies have recently been carried out on the cumulative pregnancy and ongoing pregnancy rates following assisted conception after sperm washing. The studies show that overall, a pregnancy rate (PR) and ongoing pregnancy rates per couple of 45.4% and 36.3% have been achieved with 127 clinical pregnancies, 102 infants born, and 12 pregnancies ongoing with no reported seroconversions (Nicopoullos 2010b). For combined IVF, ICSI, and frozen embryo transfer cycles, cumulative pregnancy rates and ongoing pregnancy rates per transfer of 33.0% and 26.8% were achieved (Nicopoullos 2010b). In the United States of America (Columbia University, New York), an overall clinical pregnancy rate and ongoing pregnancy rate per transfer of 46% and 39% has been achieved (Sauer 2009). These IUI success rates, as well as the IVF/ICSI rates compare favourably with IUI/IVF/ICSI with such treatments in sero-negative couples.

Description of the intervention

Semen samples are obtained by masturbation after 4 to 7 days of sexual abstinence. After liquefaction at room temperature, semen parameters are assessed as outlined by the World Health Organization (WHO) criteria (WHO 1999). Semen analysis is then performed. In the literature, there are two techniques of sperm washing. The Semprini technique and a revised technique from Messeguer. In the revised technique by Messeguer, the semen is fractionated by gradient centrifugation to separate motile spermatozoa from non-sperm cells, immotile spermatozoa and seminal plasma, after which the fraction containing sperm and nongerminal cells is re-suspended and re-centrifuged. The pellet from this second centrifugation is re-suspended in a small volume of buffer for the “swim up” procedure. In this step, the motile spermatozoa move up into the buffer and are thereby separated from non-motile, nongerminal cells. The motile fraction is collected as the purified sperm preparation. It should be noted that some reproductive units use fresh semen while in others only frozen semen is used for sperm washing (Marina 1998). In the technique reported by Semprini, the pellets are not re-suspended (Semprini 1992). From September 2008, a modified protocol of two washes, with a swim-up performed only if the patient was not on HAART or if the sample was prepared with significant debris, (white blood cells etc.), was introduced by a landmark paper by Vourliotis et al (Vourliotis 2009). This was introduced to maximize the post-wash sperm yield with no increase in residual virus demonstrated.

After sperm washing, there is no certainty that the final concentrate does not contain HIV. For this reason, after the process is completed, an aliquot is analysed by polymerase chain reaction (PCR) to rule out the presence of HIV in the semen. Only seminal samples with negative HIV-PCR results will be used for assisted reproduction procedures. After making sure the sperm is devoid of HIV, pregnancy can then be achieved with IUI, IVF or ICSI.

How the intervention might work

Accumulated data indicate that human gametes are probably not susceptible to HIV infection. The lack of CD4, CCR5 or CXCR4 receptors (to which HIV attaches when infecting a target cell) on the surface of spermatozoa is a solid argument in favour of this assumption (Baccetti 1998; Dussaix 1993). However, there are sporadic reports of recognition of viral particles associated with spermatozoa by electron microscopy, or detection of HIV-

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DNA by PCR in preparations of spermatozoa. The current view is that the main location of the HIV inoculate in semen is at the seminal plasma (as free virions) and in non-spermatic cells (epithelial cells or lymphocytes).(Mermin 1991; Pudney 1991). Hence, semen processing techniques used in assisted reproduction have been modified for use in separating spermatozoa from infectious elements in semen (Al Khan 2003). The final objective of these "sperm washing" techniques is to obtain a spermatozoa fraction that is free from HIV or HIV-infected cells which, as stated, may be found in seminal plasma or in the nongerminal cell fraction of semen, respectively.

Why it is important to do this review

The clinical value of sperm washing and its negligible or null risk were first reported in 1992 (Semprini 1992). Since then, sperm washing techniques have substantially changed the paradigm of fathering children in sero-discordant couples for male HIV infection. Also, different individual studies have reinforced the methodological (Marina 1998; Anderson 1999; Gilling-Smith 2000) and clinical issues (Ohl 2003; Pena 2003; Bujan 2004; Garrido 2004; Nicopoullos 2004; Mencaglia 2005) of sperm washing in preventing HIV transmission but allowing conception in HIV sero-discordant couples. Furthermore, an estimate of the use of sperm washing in Europe (Gilling-Smith 2000; Savasi 2006) provided additional evidence of the clinical value of this procedure. These results brought assisted reproduction into a new era, from the report of the Centers for Disease Control (CDC 1990). The 1990 recommendation from the Centers for Disease Control and Prevention (CDC) was against insemination of HIV negative women with HIV-positive semen that has been washed to decrease viral load (CDC 1990) . This stemmed from a case of HIV transmission to a female partner of an HIV infected man after intrauterine insemination of processed sperm. To be more stringent on preventing transmission of HIV infection, centres where sperm washing are currently practiced in the United States rely on the use of ICSI. The argument in favour of this is to minimize oocyte contact with seminal plasma and cells by the use of only a single sperm per oocyte. Despite these landmark achievements with sperm washing, we could not find any meta-analyses or systematic reviews assessing the benefits and harms of sperm washing on our subject of interest, thus the importance of this systematic review.

OBJECTIVES

To determine the benefits and harms of sperm washing of HIV-infected males when used to prevent the transmission of HIV but allowing conception in the HIV-negative female

METHODS

Criteria for considering studies for this review

Types of studies

We preferentially looked for randomised or quasi-randomised controlled trials on sperm washing, aimed at preventing HIV transmission and allowing conception, irrespective of publication status, year of publication, or language in the review.

Types of participants

Sero-discordant couples (HIV-positive males and HIV-negative females only).

Types of interventions

Experimental Intervention

- Sperm washing

Comparison

- No Intervention

Types of outcome measures

Primary outcomes

1.Serologic signs of HIV infection in the female partners and newborns following sperm washing:

- Females with HIV antigen-positive laboratory result.

- Females with HIV antibody-positive laboratory result.

- Newborn with HIV-positive antigens

- Newborn with HIV-positive antibodies.

Any combinations of the above results

2. Pregnancy rates following sperm washing by intrauterine insemination, intracytoplasmic sperm injection and In-vitro fertilisation and embryo transfer.

Secondary outcomes

1. Presence of adverse events in the mothers following sperm washing
2. Cost-effectiveness of treatment

Search methods for identification of studies

Electronic searches

We searched the *Cochrane HIV/AIDS Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials*, *MEDLINE*, *EMBASE*, *SCOPUS*, *AIDsearch*, *AJOL*, *LILACS* and *INDEX MEDICUS* (Royle, 2003)

We also searched the following conference proceedings for relevant abstracts:

1) The International AIDS Conference

2) The Conference on Retroviruses and Opportunistic Infections

3) The British HIV Association (BHIVA) Conference

4) The International Conference of Obstetricians and Gynecologists (FIGO)

5) The American Academy of HIV Medicine Conference

6) The Australasian HIV/AIDS Conference

7) The American Society for Reproductive Medicine (ASRM) conference

8) The European Society for Human Reproduction and Embryology (ESHRE) conference

9) The British Fertility Society (BFS) conferences

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There were no language restrictions in the searches.

Searching other resources

1) Reference lists of all papers and relevant reviews were identified.

2) Authors of relevant papers were contacted regarding any further published or unpublished work.

Data collection and analysis

We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and the *Cochrane HIV/AIDS Group Module*.

Selection of studies

Titles and abstracts of studies were screened for inclusion by two authors (AE and CO). Two authors (CO and AE) independently applied the inclusion criteria to retrieve the full text of the selected studies. Disagreements about inclusion was discussed among the two authors. We sought further information from the authors where papers contained insufficient information to make a decision about eligibility. We scrutinised each of the trials to ensure that multiple publications from the same trial are included only once. We listed the excluded studies and the reason for their exclusion.

Data extraction and management

We designed a data extraction form. Data were extracted independently by the three reviewers using the agreed upon form. The following information were extracted from each of the studies: (1) study details: citation, study population, demographics, study design, type of intervention, population size and attrition rate and (2) outcome details: HIV test results in the females and neonates, efficacy and adverse effects of sperm washing. Any disagreement were resolved through discussion among the reviewers. In the case of missing or unclear data, the authors of the publication were contacted.

Assessment of risk of bias in included studies

No relevant trials were identified for inclusion in this review .The Cochrane Collaboration domains for assessing risk of bias were planned for use in determining the risk of bias of all eligible studies. The domains, which are listed below, were to be assessed by all authors.

Sequence generation
- Adequate, sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are also adequate if performed by an independent adjudicator.

- Unclear, the trial is described as randomised but the method of sequence generation was not specified.

- Inadequate, the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for the assessment of harms.

Allocation concealment
- Adequate, allocation was controlled by a central and independent randomisation unit, serially numbered, opaque and sealed envelopes, or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.

- Unclear, the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.

- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for the assessment of harms.

Blinding
- Adequate, the trial was described as blinded, the parties that were blinded and the method of blinding was described so that knowledge of allocation was adequately prevented during the trial.

- Unclear, the trial was described as double blind, but the method of blinding was not described so that knowledge of allocation was possible during the trial.

- Not performed, the trial was not blinded so that the allocation was known during the trial.

Incomplete outcome data
- Adequate, the numbers and reasons for dropouts and withdrawals in all intervention groups were described or, if it was specified, that there were no dropouts or withdrawals.

- Unclear, the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

- Inadequate, the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting
- Adequate, predefined or clinically relevant and reasonably expected outcomes are reported on.

- Unclear, not all predefined or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.

- Inadequate, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Baseline imbalance
- Adequate, if there was no baseline imbalance in important characteristics.

- Unclear, if the baseline characteristics were not reported.

- Inadequate, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Early stopping
- Adequate, if sample size calculation was reported and the trial was not stopped, or the trial was stopped early by formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low.

- Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.

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- Inadequate, if the trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.

Trials that are assessed as being 'adequate' in all the above bias risk domains will be defined as trials with low risk of bias, and trials that are assessed as being 'inadequate' or 'unclear' in any of the above bias risk domains will be defined as trials with high risk of bias.

Measures of treatment effect

No relevant trials were identified for inclusion in this review. We had planned to use the risk difference as the measure of treatment effect for dichotomous data and standardised mean difference as the measure of treatment effect for continuous data, where applicable.

Unit of analysis issues

No relevant trials were identified for inclusion in this review. The number of participants randomised were to be used to calculate estimates of intervention effects and confidence intervals. In studies with cluster randomised trials, the unit of analysis was to be the cluster.

Dealing with missing data

No relevant trials were identified for inclusion in this review.

Assessment of heterogeneity

No relevant trials were identified for inclusion in this review. We were to assess heterogeneity and determine statistically significant heterogeneity using a Chi^2 test. Clinical, methodological, and statistical heterogeneity were to be assessed. We were to enter the studies into Review Manager 5 (RevMan 2008) and present them on forest plots.

Assessment of reporting biases

No relevant trials were identified for inclusion in this review. We were to assess for reporting bias (if greater than 10 studies were included in our review) and construct a funnel plot to look for evidence of publication bias. We were to scrutinise each of the trials report to ensure that multiple publications from the same trial are included only once. We had planned to ensure that all studies fulfilling the inclusion criteria were included into the review, irrespective of the language of publication. We were to check additional unpublished data for further information.

Data synthesis

No relevant trials were identified for inclusion in this review. We had planned to perform the meta-analyses according to the recommendations of The Cochrane Collaboration (Higgins 2008). The analyses were to be performed using Review Manager 5 (RevMan 2008). Data were to be analysed using the intention-to-treat principle where there are patients with missing data. The number-needed-to-treat was to be calculated as 1/((1-relative risk) control group event rate), where applicable (where both fixed-effect model and random-effects model are statistically significant). Both fixed-effect model and random-effects model will be used. All results were to be reported using fixed-effect model. However, when the two models give different results, both results were to be reported. Statistical heterogeneity was to be assessed by intersection of funnel plots and calculating the standard Chi^2 test, defining significance as $P < 0.05$.

Subgroup analysis and investigation of heterogeneity

No relevant trials were identified for inclusion in this review. We had planned to investigate heterogeneity using a sub-group analysis. We had planned to analyse the various ways to achieve pregnancy following sperm washing - intrauterine insemination (IUI), in vitro fertilisation and embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI).

Sensitivity analysis

No relevant trials were identified for inclusion in this review. If there are sufficient data, we had planned to perform sensitivity analyses based on the risk of bias and missing data.

RESULTS

Description of studies

No trials have been identified which are eligible for inclusion in the review. The trials listed as 'Excluded studies' were not eligible for inclusion because they were neither randomised controlled trials nor quasi-randomised controlled trials

Results of the search

No trials eligible for inclusion in this review have been identified

Included studies

No trials eligible for inclusion in this review have been identified.

Excluded studies

The trials listed as 'Excluded studies' were not eligible for inclusion because they were neither randomised controlled trials nor quasi-randomised controlled trials (Baccetti 1991; Baeten 2003; Bagasra 1994; Barnhart 2009; Barreiro 2006; Bujan 2004; Castilla 2005; Chen 2001; De Vincenzi 1994; Frodsham 2006;Garrido 2004; Gilling-Smith 2000; Gilling-Smith 2006; Kashima 2009; Mandelbrot 1997; Marina 1998; Matthews 2010; Mencaglia 2005; Nicopoullos 2004; Nicopoullos 2010a; Nicopoullos 2009a;Ohl 2003; Pasquier 2006; Pena 2003; Politch 2004; Quayle 1997; Quayle 1998; Ryder 2000; Sauer 2006; Sauer 2009; Savasi 2006; Savasi 2008; Scandlyn 2000; Semprini 1992; Semprini 2007;Stanitis 2008; Sunderam 2008;Van Leeuwen 2007; Van Leeuwen 2009; Vernazza 2006; Vourliotis 2009; Zhang 1998)

Risk of bias in included studies

No trials eligible for inclusion in this review have been identified.

Allocation

No trials eligible for inclusion in this review have been identified.

Blinding

No trials eligible for inclusion in this review have been identified.

Incomplete outcome data

No trials eligible for inclusion in this review have been identified.

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Selective reporting

No trials eligible for inclusion in this review have been identified.

Other potential sources of bias

No trials eligible for inclusion in this review have been identified.

Effects of interventions

No trials eligible for inclusion in this review have been identified.

DISCUSSION

Over 18 years after the discovery of sperm washing to prevent HIV transmission in sero-discordant couples, there are no randomised controlled trials to assess the efficacy of the procedure. There is evidence to show that the procedure has not led to seroconversions in women or their offspring after years of follow-up. However, the strength of the evidence is limited to data from observational studies. A systematic review was conducted to analyse the effectiveness and safety of washing the semen of HIV-positive men so that they can be used in assisted reproductive techniques (ART). Twenty-three studies (16 clinical series and 7 before-and-after studies) were selected, most of which were performed in Europe. The methodological limitations of the studies used for the review were identified (Bujan 2007).

There are certain reasons why a randomised trial has not been performed in this area of Reproductive Medicine. The greatest reason is due to ethical concerns about possible HIV transmission from infected men to their partners. It is neither ethically nor legally justifiable to exclude individuals from infertility services on the basis of male HIV infection. There is also the difficulty of selection of appropriate treatment and control groups. Other impediments include lack of acceptability of sperm washing program by various centres and differences in the type of assisted reproductive treatments used in the sperm washing program across continents (ICSI is the method of choice in the United States and IUI, IVF and ICSI are the methods of choice in Europe). Other reasons include the cost of sperm washing, IUI, IVF and ICSI (especially so in developing countries of Africa), treatment modalities and regulatory issues in HIV management.

Most men who are recruited for sperm washing programs or who desire sperm washing are usually on antiretroviral medications. Protocols, for the cut-off CD4 or viral load levels to be met before sperm washing can be done for HIV-positive men, differ in different treatment Centers around the world. In some Centers, HIV-positive men must have undetectable viral loads before treatment (regardless of their general well-being and clinical need for HAART). This is aimed at excluding the possibility of HIV transmission from the HIV-positive male to the HIV-negative female. In some other Centers like in the United Kingdom (Nicopoullos 2010b) and in some Centers in the United States, men require evidence of stable HIV disease for at least, 6 months. This is as evidenced by stable viral load (less than 50,000 copies per milliliter) and CD4 counts greater than 250 cells per cubic millimetre (Sauer 2009).

In recent times, certain concerns have been raised about the effects of antiretroviral medications on seminal fluid parameters. The effects of antiretroviral use by HIV-positive men to reduce viral load has shown mixed results from different studies. Some studies have shown the detrimental effect of HIV on semen parameters, with a negative correlation between CD4 cell count and semen parameters. Nicopoullos et al demonstrated the potential negative effect of the use of HAART on sperm, which may counteract the benefits of a reduction in viral load and an increase in CD4 cell count (Nicopoullos 2010c). Another study assessed 26 males and reported an overall increase in sperm motility and normal morphology, with no effect on sperm count (Robbins 2001). The effects of both the HIV disease process and the use of HAART remain uncertain. Some explanations for decreased semen parameters in HIV-positive males include a direct viral effect on spermatogenesis and an altered seminal plasma composition. These, when present, may affect the quality of sperm used for sperm washing.

Apart from the concerns of HAART on seminal fluid, there has also been a recent controversy with regard to the safety of unprotected intercourse in those with well controlled antiretroviral medications and a negative serum viral load. In sero-discordant couples where the male is infected and the female partner is not, the risk of acquisition of the HIV virus is approximately 0.1% to 0.2% per unprotected act (Mastro 1996). In a series of 104 pregnancies achieved through natural conception in HIV-positive men with HIV-negative women partners, no seroconversions occurred within the first three months following conception. However, two women seroconverted at seven months of pregnancy and two others converted postpartum (Mandelbrot 1997). However, these studies were performed before viral load testing became widely available, so the viral load status of these men were unknown.

In the wake of viral load and CD4 testing, Vernessa et al, the authors of the “Swiss statement” argued that the risk of sexual transmission of HIV can be negligibly low if three conditions are met: (1) the HIV-infected patient is receiving antiretroviral therapy with excellent adherence; (2) blood viral load levels have consistently been undetectable to less than 40 copies per millilitre for more than 6 months; and (3) no sexually transmitted diseases are present in either of the partners (Vernazza 2008). They argue that when these three criteria are met, the risk of transmission is negligible. Hence, the HIV-negative female can decide whether she wants to stop using barrier methods like condoms with her HIV-positive partner and accept the residual risk of HIV transmission. Vanessa et al stated that HIV-positive individuals without additional sexually transmitted diseases and on effective antiretroviral therapy are sexually non-infectious (Vernazza 2008).

However, despite this assertion by Vernassa et al that the risk of HIV transmission from people on effective antiretroviral therapy is negligible, there are very few studies to provide empirical evidence. Although this has been advocated by some, recent data from a large cohort of sperm washing cycles (Nicopoullos 2010c) confirm that almost 10% of men with undetectable serum viral levels were shown to have significant viral loads in their seminal samples. Again, even though HIV might be undetectable in blood, it can be present in semen or genital fluids at infectious levels (Kalichman 2008) David Wilson and colleagues in another study showed that the risk of HIV transmission in the presence of effective HAART treatment is low, but does not totally eliminate the risk of viral transmission (Wilson 2008). They argued that certain factors can reduce the effectiveness of anti-viral treatment. These include the degree of viral suppression, treatment failure, viral blips and the presence of other sexually transmitted infections. They also argued that in the presence of other sexually transmitted infection (STIs), the baseline risk of HIV transmission is higher. Wilson et

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al therefore, advised that the use of barrier methods should still be encouraged even when the viral load remains undetectable. Even though from their study, they found that the effectiveness of treatment in reducing the risk of HIV transmission per sexual act was about the same as has been reported for condoms, they concluded by a word of caution for global HIV prevention -"there is a major difference between small and zero risk" (Wilson 2008). They encouraged clinical researchers internationally to join forces to investigate the risk of HIV transmission from people undergoing effective antiretroviral treatment.

Another important concern is the issue of compartmentalisation of the HIV virus. Compartmentalisation tries to define different relationships between the HIV virus in blood and the genital tract. Data support the hypothesis that HIV replication is compartmentalised within the female genital tract during antiretroviral therapy. This has implications for pathogenesis and for epidemiologic surveillance for HIV. It has been shown that blood and genital tract viral loads may not correlate well, such that even a low blood viral load may not translate into low semen viral loads (Kim 1999). The absence of a correlation between plasma and semen viral load suggest that semen and blood are distinct viral compartments. In a study by Liuzzi et al, viral load in semen was not related to the clinical stage of HIV infection or to the CD4+ lymphocyte count (Liuzzi 1996). In another study by De Pasquale et al, resistant HIV virus was detected concordantly in blood and genital tract specimens, consistent with drug selection pressure in both compartments. However, drug-selected mutations differed in each compartment, and phylogenetic analysis showed differences in virus lineage in these compartments (De Pasquale 2003). Further studies by Coombs et al showed lack of association between culturability of the HIV virus in semen and viral RNA level in blood, discordant distribution of viral phenotypes, discordant viral RNA levels, a weak correlation between viral RNA levels in semen and CD4 cell count in blood, differences in the biologic variability of viral RNA levels and differences in the virus load response to antiretroviral therapy (Coombs 1998). These are all issues to consider when counselling HIV sero-discordant couples.

Therefore, it has to be reiterated that even though there may not be randomised controlled trials to prove that sperm washing decreases transmission of HIV to the female partners and allow conception, the potential risks of not performing sperm washing need to discussed with sero-discordant couples. The lack of seroconversion in studies done in Europe and the United Kingdom show that sperm washing is safe, if done properly. This should also be discussed with couples. Also, evidence from observational data is in keeping with worldwide data for similar fertility treatments in the HIV-negative population. The main outcome of note is the risk of transmission. There has been arguments that there is no role for a randomised controlled trial in comparing pregnancy outcomes since management would be in line with the HIV-negative population.

In the absence of any relevant randomised controlled trial evaluating sperm washing to prevent HIV transmission from HIV infected men but allowing conception in sero-discordant couples, this review identifies the need for randomised controlled trials to assess the benefits and possible risks of sperm washing in preventing HIV transmission from HIV-infected men but also allowing conception in sero-discordant couples. Possible future randomised controlled trials on sperm washing could consider the efficacy of the different assisted reproductive treatments like IUI, IVF and ICSI across continents. It cannot be overemphasised that sperm washing is invaluable in the current day management of HIV patients in fertility clinics.

Summary of main results

No trials eligible for inclusion in this review have been identified.

Overall completeness and applicability of evidence

No trials eligible for inclusion in this review have been identified.

Quality of the evidence

No trials eligible for inclusion in this review have been identified.

Potential biases in the review process

No trials eligible for inclusion in this review have been identified.

Agreements and disagreements with other studies or reviews

No trials eligible for inclusion in this review have been identified.

AUTHORS' CONCLUSIONS

Implications for practice

Due to lack of randomised controlled trials on sperm washing to prevent transmission from HIV infected men but allow conception in sero-discordant couples, conclusions about the efficacy of sperm washing at present, are from observational studies. Though many studies have reported high success rates, and a systematic review has been carried out (Bujan 2007), the evidence is currently limited to observational studies. Clinicians should therefore inform HIV-infected couples about the current issues surrounding sperm washing if it is to be used, and counsel them appropriately.

Implications for research

The absence of randomised controlled trials evaluating sperm washing to prevent HIV transmission from HIV positive men as shown by this extensive literature search suggests the need for a well-designed prospective randomised controlled trial in order to make unflinching recommendations regarding its use. Even though results support the view that assisted reproduction with sperm washing should not be denied to sero-discordant couples in developed countries and, where possible, could perhaps be integrated into a global public health initiative against HIV in developing countries, there is still room for more research in this area. The challenges in this area of HIV research are enormous.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baccetti 1991	Not a RCT/quasi-RCT
Baeten 2003	Not a RCT/quasi-RCT
Bagasra 1994	Not a RCT/quasi-RCT
Barnhart 2009	Not a RCT/quasi-RCT
Barreiro 2006	Not a RCT/quasi-RCT
Bujan 2004	Not a RCT/quasi-RCT
Castilla 2005	Not a RCT/quasi-RCT
Chen 2001	Not a RCT/quasi-RCT
De Vincenzi 1994	Not a RCT/quasi-RCT
Frodsham 2006	Not a RCT/quasi-RCT
Garrido 2004	Not a RCT/quasi-RCT
Gilling-Smith 2000	Not a RCT/quasi-RCT
Gilling-Smith 2006	Not a RCT/quasi-RCT
Kashima 2009	Not a RCT/quasi-RCT
Mandelbrot 1997	Not a RCT/quasi-RCT
Marina 1998	Not a RCT/quasi-RCT
Matthews 2010	Not a RCT/quasi-RCT
Mencaglia 2005	Not a RCT/quasi-RCT
Nicopoullos 2004	Not a RCT/quasi-RCT
Nicopoullos 2009	Not a RCT/quasi-RCT
Nicopoullos 2009a	Not a RCT/quasi-RCT
Nicopoullos 2010a	Not a RCT/quasi-RCT
Ohl 2003	Not a RCT/quasi-RCT

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Study	Reason for exclusion
Pasquier 2006	Not a RCT/quasi-RCT
Pena 2003	Not a RCT/quasi-RCT
Politch 2004	Not a RCT/quasi-RCT
Quayle 1997	Not a RCT/quasi-RCT
Quayle 1998	Not a RCT/quasi-RCT
Ryder 2000	Not a RCT/quasi-RCT
Sauer 2002	Not a RCT/quasi-RCT
Sauer 2006	Not a RCT/quasi-RCT
Sauer 2009	Not a RCT/quasi-RCT
Savasi 2006	Not a RCT/quasi-RCT
Savasi 2008	Not a RCT/quasi-RCT
Scandlyn 2000	Not a RCT/quasi-RCT
Semprini 1992	Not a RCT/quasi-RCT
Semprini 2007	Not a RCT/quasi-RCT
Stanitis 2008	Not a RCT/quasi-RCT
Sunderam 2008	Not a RCT/quasi-RCT
Van Leeuwen 2007	Not a RCT/quasi-RCT
Van Leeuwen 2009	Not a RCT/quasi-RCT
Vernazza 2006	Not a RCT/quasi-RCT
Vourliotis 2009	Not a RCT/quasi-RCT
Zhang 1998	Not a RCT/quasi-RCT

FEEDBACK

US clinics and research centers provide spermwashing/IUI for HIV sero-discordant couples, 16 February 2011

Summary

We were pleased to see the Cochrane Review Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples by Eke and Oragwu. This review will become a crucial reference in the emerging dialogue on safer conception options for sero-discordant couples in the US. We would like to correct the authors statement that sperm washing is only offered in conjunction with In vitro fertilisation (IVF)/Intracytoplasmic sperm injection (ICSI) in the US. While the CDC has not yet reversed its 1990 recommendation against the use of intrauterine insemination (IUI) based on a single case report of HIV transmission, there are now several US clinics and research centers that have followed the lead of European centers and are now offering sperm washing/IUI to HIV sero-discordant couples. The National Perinatal HIV Hotline based at UCSF maintains a database of US clinics providing assisted reproduction

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services to sero-discordant couples. The hotline provides information to clinicians and patients as well as facilitates referrals to clinics providing specialized care for sero-discordant couples seeking conception. Those interested in additional information can contact the National Perinatal HIV Hotline coordinator, Shannon Weber, sweber@nccc.ucsf.edu or 1-415-206-4241

Reply

Thank you Dr. Deborah Cohan and Shannon Weber for your interest in this review, and for your important comments. It is interesting to know that there are now several US clinics and research centers that have followed the lead of European centers and are now offering sperm washing/IUI to HIV sero-discordant couples. While we tried to find these centers through the web and through scientific databases, we realized that these centers could be easily be reached through the National Perinatal HIV Hotline based at University of California, San Francisco, USA. This center maintains a comprehensive database of US clinics providing assisted reproduction services to sero-discordant couples and the various assisted reproductive treatment options available in US hospitals. The Perinatal HIV Hotline launched in 2011, in collaboration with the Infectious Disease Society of Obstetricians & Gynecologists (IDSOG) and the University of California, San Francisco Fellowship in Reproductive Infectious Diseases, a ReprolDHICV Listserv as a forum for clinicians to discuss clinical cases, find patient referrals, share protocols and network with colleagues. As noted by Shannon, Those interested in getting additional information about these centers, their location and the type of ART they offer can contact the National Perinatal HIV Hotline coordinator in the United States, Shannon Weber at sweber@nccc.ucsf.edu or 1-415-206-4241. Thank you.

Dr Eke AC & Dr Oragwu CI.

Contributors

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WHAT'S NEW

Date	Event	Description
16 March 2011	Feedback has been incorporated	Author response to feedback added.

HISTORY

Protocol first published: Issue 4, 2010
Review first published: Issue 1, 2011

Date	Event	Description
16 February 2011	Feedback has been incorporated	Feedback added.

CONTRIBUTIONS OF AUTHORS

Eke Ahizechukwu Chigoziem and Chikelue Ifeanyi Oragwu carried out the review. All authors agreed on the final version.

DECLARATIONS OF INTEREST

We declare that we have no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No support was received for this review, Not specified.

External sources

- No support was received for this review, Not specified.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review contains the abstract, discussion and the list of excluded studies. No studies met the inclusion criteria. Forty four studies were excluded because they were not randomised controlled trials or quasi-randomised controlled trials.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fertilization; *HIV Seronegativity; *Sperm Retrieval; HIV Infections [*prevention & control] [transmission]

MeSH check words

Female; Humans; Male

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