RESEARCH ARTICLE

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Effects of Human Immunodeficiency Virus infection on Reproduction and Fertilty of HIV positve males

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ABSTRACT

The HIV that leads to AIDS has infected 60 million people worldwide causing 25 million deaths since it was discovered in humans in 1981. More than 80 percent of human immunodeficiency virus infections are transmitted via sexual intercourse. In males the HIV infection is associated with infectious semen and the risk of virus transmission. Semen quality deteriorates with the progression of immunodeficiency. The most relevant source of HIV in the male reproductive tract is infected leukocytes (lymphocytes, monocytes, macrophages). Studies suggest that the controversy regarding the fact that the virus also infects spermatozoa still need further investigations. In AIDS patients, grossly abnormal sperms and leukocytospermia have been reported. According to a study the disturbed functions of seminal vesicle and prostate could explain the decrease volume as well as the more viscous semen found in HIV infected subjects. In HIV infections testicular function deteriorates with progression of immunodeficiency. The mechanism by which HIV infection alters sperm parameters remains unclear. Little data are available to clarify the specific role of HIV in fertility. Researchers hypothesize that the Virus not only plays a direct role in reduced fertility among HIV-positive patients, but also has an indirect impact for positive women and men. Reproduction in this situation needs special counseling and experience, as HIV transmission is likely to increase as more infected individual chose to have children with their HIV negative partner. Recent literature has demonstrated that it is not only technically possible, but also safe to utilize sperm washing techniques to allow for the creation of embryos, thereby preventing transmission of HIV and allows HIV positive men to father children with minimizing the risk of viral transmission. Studies still suggest need of further research on all these aspects.

Keywords: *Fertility, Male, HIV*

MALE INFERTILITY:

This is when a man produces no, or has a very little sperm count. It can stop couples having babies, and sometimes be caused by another more serious STI or sexually transmitted disease. Misconceptions are very common in the world of infertility. One popular myth is that infertility is the woman's problem and that once that "problem" is fixed, the couple will be able to conceive. This could not be farther from the truth. In fact, in nearly 30% of all infertility cases, the cause is attributed to a factor in the male and in an additional 30% of cases the cause is attributed to both male and female factors.

Estimates state that as many as 15% of all couples in the United States have difficulty conceiving a child. In one-third of the cases of infertility, the problem is male infertility. Roughly, 6% of men between the ages of 15 and 50 suffer from male infertility.

Most cases of male infertility are the result of abnormal sperm count or low sperm quality. Although it takes only one sperm to fertilize an egg, an average ejaculation contians nearly 200 million sperm. The natural barriers in the female reproductive tract prevent all but about 40 sperm from reaching the egg. The number of sperm in an ejaculation and the degree of fertility are strongly correlated.

Decreased sperm production is the cause of about 90% of cases involving low sperm counts. Unfortunately, an about 90% of these cases, the cause of deficient sperm production can't be found. Two conditions are associated with insufficient sperm:

oligospermia and azoospermia. The first refers to a low sperm count while the second is an absence of living sperm in the semen.

Sperm count as well as sperm quality has been decreasing over the last few decades. In 1940, the average sperm count was 113 million per milliliter; by 1990, the value had dropped to 66 million. Adding to this problem, the amount of semen fell almost 20%, from 3.4 milliliters to 2.75 milliliters. Taken these findings together, it tells us that per each ejaculation, men are now supplying only about 40% of the number of sperm men supplied in 1940.

The downward trend in sperm count has led to speculation that recent environmental, dietary, or lifestyle changes are interfering with a man's ability to manufacture sperm. Although the speculation is controversial, substantial evidence supports it.

There are a number of potential problems that a semen analysis can detect. They include:

1. Azoospermia. No sperm are produced, or the sperm aren't appearing in the semen.
2. Oligiospermia. Few sperm are produced.
3. Problems with sperm motility. If sperm aren't moving normally, they are less likely to be capable of fertilizing an egg.
4. Problems with sperm morphology. Problems with the form and structure -- or morphology -- of the sperm may cause infertility.

But while these conditions may be the direct reason that one can't conceive, they themselves may be caused by an underlying medical condition..

REASONS FOR MALE INFERTILITY:

There are a wide number of reasons for male infertility. Some are caused by physical problems that prevent the sperm from being ejaculated normally in semen. Others affect the quality and production of the sperm itself.

Possible problems include:

1. Sexually transmitted diseases or other infections. Genital infections such as chlamydia and gonorrhea can cause infertility in men. The infertility can often be resolved by treating the infection.
2. Blockages, birth defects, or physical damage.
3. In some cases, men are born with blockages in parts of the testicle or other abnormalities that prevent sperm from getting into the semen. Physical trauma to the testicles, prostate, and urethra (define) can also result in fertility problems. Surgery can sometimes correct the problem.
4. Retrograde ejaculation.

In this condition, semen doesn't come out of the penis during ejaculation but instead enters the bladder. It can be caused by diabetes, certain medications, and surgery to the bladder, prostate, or urethra.

OTHER FACTORS THAT MAY CAUSE MALE INFERTILITY:

Studies have shown that exercising too much may lead to the release of too many steroid hormones. This can affect fertility.

1. Stress.
2. Obesity.
3. Use of drugs, alcohol, or tobacco. Smoking tobacco, using drugs such as marijuana and cocaine, and taking steroids can reduce sperm counts.
4. Exposure to toxins and environmental hazards. Pesticides, lead, radiation, radioactive substances, mercury, and heavy metals may affect fertility.
5. Heat. Although the effect is usually temporary, high temperatures in the testicles could reduce sperm production. High heat could result from wearing clothing that's too tight and traps heat, frequent bike riding, or by taking too many hot baths or saunas.

Male Fertility and HIV:

HIV stands for 'Human Immune-deficiency Virus'. It causes AIDS (Acute Immune Deficiency Syndrome). This virus attacks immune system of the body. By immune system it is meant that system of the body which is responsible for producing different materials within the body required for fighting out different external agents like virus, bacteria, fungus and alike organisms gaining entry in the body do make harm and produce various infective diseases. HIV does not make any harm to the body until it precipitates AIDS by destroying immune system and production of immune bodies are severely hampered; so that the body cannot fight against those harmful external agents; as such suffers from various infections refusing all attempts of inducting cure whether by internal natural modes or external therapeutic mode. Fertility is concerned with reproductive system; one of the totipotent cell systems, completely different from the Immune system. HIV does not show any concern with reproductive system, so this system is not affected directly by HIV.

Results of a recent review indicate that people with HIV may be at an increased risk for infertility, due to both the virus itself and the use of antiretroviral. Results on the causes of infertility in men and women with HIV have been conflicting, but in general appear to indicate that people with HIV, particularly people with advanced HIV infections or AIDS, are less fertile than HIV-negative men and women. The effects of antiretrovirals on fertility have also been unclear. Since advanced HIV infection tends to decrease fertility, starting HAART can improve the likelihood of pregnancy. However, there are also indications that the drugs can have negative effects on fertility. The use of some antiretroviral, particularly zidovudine (Retrovir) and other older nucleoside reverse transcriptase inhibitors (NRTIs), may affect fertility in people with HIV.

Previous studies have shown that NRTIs, particularly older NRTIs, may cause damage to mitochondria, which are small structures within cells that supply cellular energy. In particular, NRTI use may damage the mitochondria in sperm and eggs, leading to infertility.

Other studies have shown that HIV-positive men on HAART may have damaged sperm, decreased sperm count, and decreased sperm motility. HIV is most common among people of reproductive age. As a result, a growing number of people with HIV desire to have children and are planning to become pregnant Attempts to determine the role of HIV itself in infertility have had mixed results. In men, studies have shown that several sexual problems that affect fertility are more common with HIV infection. Men infected with HIV, particularly men with advanced HIV, are more likely to have inflammation of the testicles and are more likely to produce insufficient testosterone levels.

Also, men with HIV are more likely to experience decreased sex drive and an estimated 60 percent experience erectile or ejaculatory dysfunction.

Sperm function also appears to be affected by HIV, with healthier men having fewer problems with their sperm. According to the review authors, men with higher CD4 (white blood cell) counts tend to have better semen volume, sperm motility, and sperm counts, all of which affect fertility, than men with lower CD4 counts.

The effects of antiretroviral on fertility have also been unclear. Since advanced HIV infection tends to decrease fertility, starting HAART can improve the likelihood of pregnancy. However, there are also indications that the drugs can have negative effects on fertility. In addition, according to the review authors, the use of some antiretrovirals, particularly zidovudine (Retrovir) and other older nucleoside reverse transcriptase inhibitors (NRTIs), may affect fertility in people with HIV. Other studies have shown that HIV-positive men on HAART may have damaged sperm, decreased sperm count, and decreased sperm motility. (Clayton, 2011).

Human Reproduction Update (2007) reports that at present, over 40 million people are infected with the human immunodeficiency virus type-1 (HIV-1). Most HIV-1-infected men and women are of reproductive age [Joint United Nations Programme on HIV/AIDS (UNAIDS), 2005]. For those who have access to highly active antiretroviral therapy (HAART), the course of HIV-1 has shifted from a lethal to a chronic disease (Barre-

Sinoussi *et al*., 1983; Yeni *et al*., 2004). As a result of this, many patients with HIV-1 infection consider having offspring, as do other patients of reproductive age with chronic illnesses (Frodsham *et al*., 2006).

In couples with one HIV-1-infected partner, that is serodiscordant couples, the uninfected partner is at risk of becoming HIV-1 infected, if trying to conceive naturally. Sexual HIV-1 transmission from men to women seems more likely than vice versa (de Vincenzi, 1994), although some studies claim similar transmission rates (Quinn *et al*., 2000). It is therefore generally accepted to advise serodiscordant couples to avoid unprotected intercourse at all times. This artificial sterility implies that serodiscordant couples with an HIV-1-infected man have to rely on assisted reproduction techniques (ART), and serodiscordant couples with an HIV-1-infected woman have to practise self-insemination, if they wish to achieve parenthood.

The exact origin of HIV-1 in the male genital tract is at present unclear. Histological studies show a loss of testicular germ cells and maturation arrest of spermatozoa during spermatogenesis (Dalton and Harcourt-Webster, 1991; Shevchuk *et al*., 1999). However, because these studies were performed in men who died of acquired immune deficiency syndrome (AIDS), these data may not be representative for asymptomatic HIV-1 infection.

HIV-1 is present in the semen of asymptomatic HIV-1-infected men as free HIV-1 RNA particles in seminal plasma and as cell-associated virus in non-spermatozoal cells (NSC) such as lymphocytes and macrophages (Lowe *et al*., 2004). Most HIV-1 RNA seem to originate from the seminal vesicles and prostate, given that a vasectomy did not influence the concentration of HIV-1 RNA in semen (Anderson *et al*., 1991; Krieger *et al*., 1998). The detection of distinct HIV-1 populations in the epididymis and prostate suggests that HIV-1 particles can be produced locally in the male genital tract (Simbini *et al*., 1998; Paranjpe *et al*., 2002; Coombs *et al*., 2003).

Early studies claimed that HIV-1 DNA was present in spermatozoa and spermatogonial stem cells (Bagasra *et al*., 1994; Nuovo *et al*., 1994; Scofield *et al*., 1994; Muciaccia *et al*., 1998), but later studies have contradicted these findings (Quayle *et al*., 1997, 1998; Pudney *et al*., 1999). In addition, the presence of HIV-1 (co)-receptors CD4, CXCR4 and CCR5, necessary for cellular entry of HIV-1, has not been demonstrated on the spermatozoal surface (Kim *et al*., 1999). Therefore, it seems unlikely that spermatozoa are directly infected with HIV-1 (Quayle *et al*., 1997, 1998; Pudney *et al*., 1999).

Intermittent shedding of HIV-1 RNA is the most common pattern of HIV-1 presence in semen. There are two explanations for this phenomenon. First, the composition of the ejaculate varies between men as well as over time within the same individual. Second, local inflammation may increase HIV-1 RNA levels in semen, independent of HIV-1 RNA concentrations in blood (Cohen *et al*., 1997; Ping *et al*., 2000).

In untreated HIV-1 infection, the concentration of HIV-1 RNA in semen is on average ~10-fold lower than that in blood plasma. Nevertheless, in some individuals, the HIV-1 RNA concentration in seminal plasma is higher than that in blood plasma (Lowe *et al*., 2004). Most antiretrovirals penetrate well into the male genital tract, except for some protease inhibitors (Taylor *et al*., 2001a; Lowe *et al*., 2004), and in general, HIV-1 RNA concentrations in blood and seminal plasma show a parallel decrease in response to HAART (Barroso *et al*., 2000; Taylor *et al*., 2001b; Leruez-Ville *et al*., 2002a).

However, intermittent shedding leads to occasional discrepancies between HIV-1 RNA in blood and seminal plasma. HIV-1 RNA can be detected in seminal plasma despite adequate suppression of HIV-1 RNA in blood, and HIV-1 RNA can be detected on and off in semen despite stable levels or even undetectable levels of HIV-1 RNA in blood (Zhang *et al*., 1998; Kim *et al*., 1999; Barroso *et al*., 2000; Gupta *et al*., 2000; Vernazza *et al*., 2000; Bujan *et al*., 2002, 2004a; Leruez-Ville *et al*., 2002a).

Thus, although of undefined origin, HIV-1 is clearly present in the male genital tract albeit at variable concentration and frequency.

Studies says that, in general, semen parameters are not impaired by asymptomatic HIV-infection (Krieger *et al*., 1991; Crittenden *et al*., 1992; Muller *et al*., 1998), although

occasionally a reduction in sperm motility and a decrease in the percentage of spermatozoa with normal morphology have been observed (Dulioust *et al*., 2002; Nicopoullos *et al*., 2004). The fact that men with and without antiretroviral therapy were analysed as one group in these studies limits these conclusions. It is therefore unclear whether the observed changes are caused by the HIV-1 infection itself or by the antiretroviral therapy.

A decrease in semen volume and sperm motility was observed in a single semen donor, of whom multiple semen samples were available before and after seroconversion for HIV-1 (van Leeuwen *et al*., 2004). The seminal vesicles, the secretions of which constitute more than 60% of the seminal fluid, could represent a major source of virus in semen. The presence of infected cells in the seminal vesicles of treated men with undetectable viremia suggests that this organ could constitute a reservoir for HIV (Deleage et al., 2011)

A longitudinal study evaluated the effect of ongoing HIV-1 infection on semen parameters. And found that none of the semen parameters changed significantly during a follow-up period of 96 weeks. However, progressive motility was low at all time points, and semen volume was in the lower normal range according to World Health Organization (WHO, 1992) criteria, in agreement with the above-mentioned semen donor. Above 200 cells/mm^3 CD4 counts were not associated with any of the semen parameters studied. Because concern for long-term side effects of antiretroviral therapy has led to postponing start of antiretroviral therapy until CD4 counts drop to 200–350 cells/mm^3 (Yeni *et al*., 2002), the data of this longitudinal study are reassuring in so far that postponing treatment does not appear to negatively affect semen parameters.

Data on semen parameters before and after antiretroviral therapy suggests that the semen parameters were normal according to WHO criteria and remained stable after administration of zidovudine (AZT) monotherapy in 5 HIV-1-infected men (Crittenden *et al*., 1992) but improved in 20 men after 4 or 12 weeks of HAART (Robbins *et al*., 2001). The observed improvement in the latter study may be because of an improved general health resulting from HAART. The follow-up in this study was too short to evaluate any potential detrimental impact of HAART on spermatogenesis, because a full round of spermatogenesis takes ~70 days.

Mitochondria are abundant in spermatozoa and necessary for progressive motility. Deletions in mitochondrial DNA of spermatozoa have been described as a result of antiretroviral therapy (White *et al*., 2001). Theoretically, penetration of nucleoside reverse transcriptase inhibitors into spermatozoa or their precursors could result in mitochondrial toxicity and thereby may lead to impaired progressive motility. This hypothesis however remains to be proved.

Normally, a healthy male produces millions of sperm each day, although only a few of these sperm will ever go on to fertilize an egg and create an embryo. Despite the vast quantity of sperm produced by a healthy man, the number of sperm which actually fulfill their fertilizing potential is therefore extremely small. Even when a man is producing sperm at a healthy capacity and his partner is fertile, it is not uncommon for couples to take up to a year to conceive.

Some men produce sperm which is suboptimal, either in quantity or quality. These men will typically take longer to conceive and are more likely to require the assistance of artificial reproduction techniques to do so. Some men may experience suboptimal sperm production because of a genetic or birth trait (e.g. deletions on the Y chromosome or history of cryptorchidism). In many cases, sperm production declines over time as a result of exposure to a range of risk factors.

Human Immunodeficiency Virus (HIV) also impacts on sperm production and semen parameters deteriorate as immunodeficiency progresses. One study reported decreased concentrations of motile sperm in HIV+ compared to HIV- men. The ways in which HIV is related to male sub-fertility is also unclear. It may be associated with decreased immune function, the effects of anti retroviral therapy medication, or co-existing genito-urinary tract infection.

Kushnir and Lewis (2011) Male infertility also can impact reproductive efficacy in HIV/AIDS. Sperm parameters that reflect fertility are significantly impaired in HIV-1 infected men. Measurements including semen volume, sperm motility, concentration and morphology are adversely affected (Leruez 2002 & 2002, Dulioust, 2002). Semen parameters correlate positively with CD4 counts (Nicopoullos et al 2010), which suggests that patients with full blown AIDS are less fertile than healthier HIV-1 infected males. HIV-1 infected men are more likely to have orchitis, hypogonadism, and leukospermia which could account for oligospermia and teratozoospermia. Barboza et al employed atomic force microscopy to examine sperm morphological and topographical changes in HIV/AIDS patients receiving HAART and revealed that damage to the spermatozoa was due to HAART rather than the HIV-1 virus (Barboza et al, 2004). These ultrastructural findings contrast earlier ones where no adverse effect on sperm resulted from AZT treatment (Politch et al, 1994). Recent data indicate that HAART significantly decreased total sperm count, progressive motility, and post-preparation count while it significantly increases the proportion of abnormal sperm forms (Nicopoullos et al., 2010).

Hypogonadism, diminished libido and impotence are major issues in HIV infected men. Erectile and ejaculatory dysfunction is estimated to affect 60% of men with advanced disease (Tindall et al, 1994. Men tend to have normal testosterone levels early in the course of HIV disease. As the disease progresses to AIDS, testosterone levels decline. Androgen deficiency is particularly common in AIDS wasting syndrome (Grinspoon S, Corcoran C, Lee K, et al, 1996). The progressive decline in testosterone has been attributed to both gonadal and extragonadal causes (Christeff et al., 1992. Croxson et al, 1989, Poretsky et al., 1995, Sellmeyer et al., 1996). Secondary hypogonadism is more commonly seen than primary hypogonadism due to testicular atrophy. However, both may lead to a similar clinical picture. It is important to measure both free and bioavailable testosterone since elevated sex hormone binding globulin levels have been observed in HIV-infected men (Martin et al., 1992).

Use of alcohol and illicit drugs may affect testosterone production (Smith & Asch,1987). Side effect of medications used in the treatment of HIV including glucocorticoids (used as appetite stimulants) and ketoconazole include suppression of the hypothalamic-pituitary-gonadal axis and inhibition of testosterone synthesis respectively (Sonino N, 1987).

Lipodystrophy is common in HIV and remains an important clinical problem. Gynecomastia may be seen in HIV-infected men in association with protease inhibitor use, liver dysfunction, and as part of lipodystrophy (Peyriere H, Mauboussin JM, Rouanet I, et al. 1999), and this is addressed in detail below. Treatment of symptomatic hypogonadal men with testosterone replacement should be considered following an appropriate investigation of the eitiology. Benefits of treatment may include improvement in body mass, strength, sexual and cognitive function, bone density, as well as quality of life (Cofrancesco J, Jr, Whalen JJ, III, Dobs AS. 1997, Bhasin S, Storer TW, Javanbakht M, et al. 2000); these are counterbalanced by serious side effects. It is important to recall that exogenous androgens inhibit spermatogenesis; therefore their use in men desiring future fertility may not be appropriate.

CONCLUSION:

Several factors like decline in testosterone levels, sperm motility, number and mitochondria of sperms necessary for progressive motility of spermatozoa as a result of antiretroviral therapy suggest an overall decline in fertility status of HIV males. The controversy regarding the fact that the virus also infects spermatozoa, and need further investigations. The mechanism by which HIV infection alters sperm parameters remains unclear. Various findings suggest that ARTs is a safe option for HIV-discordant couples, and may be safer than attempted natural conception. Need of further research on all these aspects is recommended.

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