NEW DEBATE

Is natural conception a valid option for HIV-serodiscordant couples?

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The remarkable reduction in HIV-related morbidity and mortality as a consequence of the widespread use of highly active antiretroviral therapy (HAART) has led to a growing number of HIV-infected persons and their partners requesting counselling regarding the chances of reproduction. A thoughtful medical evaluation of the couple, which should entail HIV status, screening for genital infections and fertile potential, is needed before considering any reproductive attempt. Given that both sexual and perinatal transmission of HIV is directly correlated with the level of viral replication, being almost negligible in patients with undetectable viremia, HAART should be given to the infected partner to minimize the risk of transmission. Assisted reproduction after ‘sperm washing’ may further reduce the chances of infection, although this is not within reach or desire for a significant number of HIV-serodiscordant couples. From our perspective, natural conception could now be considered a possible alternative for HIV-serodiscordant couples, as long as complete suppression of viremia with HAART is achieved in the infected partner. The objective of this paper is to propose a protocol that may minimize risks in HIV-discordant couples that have opted for natural conception.

Keywords: HIV; sexual transmission; vertical transmission; antiretroviral therapy; viral load

Introduction

Reproductive possibilities were much restricted in the first years of the HIV pandemic. For example, the Centers for Disease Control and Prevention (CDC) discouraged any reproductive attempt in HIV-infected persons due to the poor prognosis of the disease and the risk of transmission (Anonymous, 1985). Similar opinions were shared by the American College of Obstetrics and Gynecology, which recommended HIV-infected women not to become pregnant (Kass, 1994), and the American Society for Reproductive Medicine, which suggested other alternative options such as donor insemination or child adoption (Anonymous, 1994). However, even in those difficult times, many HIV-positive individuals chose to seek pregnancy, assuming the risk of sexual and/or vertical transmission of HIV (Selwyn et al., 1989).

The provision of antiretrovirals in triple combination, the so-called highly active antiretroviral therapy (HAART), which allows complete suppression of viral replication and significant improvement of the immune status in most patients, has dramatically changed the natural history of the disease. HIV infection may be now considered a chronic illness for most carriers, at least in developed countries (Gallant, 2000). As a consequence, HIV-infected individuals can look forward to an active and productive life style, the possibility of bearing healthy children being an important issue.

The major change is that the reduction of viral replication under HAART greatly impacts on the risk of sexual and vertical HIV transmission. In fact, the CDC reviewed in 2001 their previous statements, concluding that now healthcare professionals should ‘provide information and give support to any reproductive option for HIV-positive patients’, particularly when HIV infection is under medical control (Centers for Disease Control and Prevention, 2001). Patient’s perspective has also shifted, and heterosexual couples are now more likely to consider the chances of having their own children (Riley and Yawetz, 2005). As an example, a recent study that examined >1200 heterosexual HIV-infected persons of reproductive age showed that considering women and men separately, respectively, 45 and 30%, were already parents, 3 and 1%, were expecting a baby, 6 and 6% were seeking a pregnancy and 32 and 20% admitted desires for future pregnancies. In the multivariate analysis, the desires for having children were 2.6 and 1.9 times greater in women and men, respectively, without descendents. Of note, 76% of women and 62% of men...
were part of HIV-serodiscordant couples, namely the other partner was HIV-negative (Heard et al., 2007). The growth in plans for pregnancy among HIV-infected individuals along the HAART era has been highlighted in several other reports (Schuster et al., 2000; Chen et al., 2001; Klein et al., 2003; da Silveira et al., 2005).

Assisted reproduction

Another consequence of this desire for children and the achievements of HAART is that HIV-positive persons may be now considered for assisted reproductive technology (ART). In one study, the proportion of specialists ready to offer these techniques to HIV-positive women with fertility problems increased from 3 to 47% between 1993 and 2000 (Englert et al., 2001). There is growing consensus to assist HIV-infected women in reproduction programmes, given that the risk of HIV vertical transmission along pregnancy is still a major concern (Savulescu, 2003; Zutlevics, 2006). If the male partner is the one infected, assisted reproduction is generally more readily accepted as a way to further minimize the chance of HIV sexual transmission which, even without any medical intervention, is still lower than the risk for vertical transmission.

There is wide experience with ‘sperm washing’ prior to intrauterine insemination (IUI), IVF or ICSI. The main location of the HIV inoculate in the male genital tract is seminal plasma (as free virions) or non-spermatic cells (epithelial cells or lymphocytes) (Mermin et al., 1991; Pudney and Anderson, 1991), so that use of a spermatozoa concentrate for subsequent ART would be safe in terms of HIV transmission (Chrystie et al., 1998; Al Khan et al., 2003). The results from two large series of HIV-serodiscordant couples undergoing ‘sperm washing’ procedures have recently been released. The one by Sauer (2005) comprises 1111 and 352 women undergoing IUI and IVF/ICSI. The rate of successful pregnancies, according to total number of newborn babies, was 12% per cycle and 32% per couple after IUI; the percentages were 24% per cycle and 37% per couple for IVF/ICSI. Reproductive outcomes in the study by Savasi et al. (2007), in which 741 couples were analysed, were fairly similar; the pregnancy rates for IUI were 19% per cycle and 78% per couple, and for IVF/ICSI were 23% per cycle and 41% per couple. Similar results have been reported by others (Marina et al., 1998; Sauer and Chang, 2002; Ohl et al., 2003; Bujan et al., 2004b; Semprini et al., 2004; Vernazza et al., 2006). The reproductive efficacy of ART after ‘sperm washing’ does not seem to be significantly affected by the additional manipulation of the semen. Thus, initial reports on IUI with donor sperm to avoid HIV transmission attained a 25% pregnancy rate per cycle (Garrido et al., 2002). Also, the 2003 results from the Canadian ART register show a rate of clinical pregnancy per IVF/ICSI cycles of 31.2% in seronegative individuals (Gunby et al., 2007).

Usually, more than one reproductive procedures are needed to attain pregnancy (Gilling-Smith et al., 2006), which increases the final cost of ART. In general, the substantial expenses per procedure make these methods not affordable for a significant proportion of HIV-infected persons, or hinder the public health system coverage in many countries. Some technical constraints also contribute to limit the implementation of this technology for HIV-infected individuals, as separate laboratory facilities are required to avoid cross-contamination to uninfected patients (Englert et al., 2001; Gilling-Smith et al., 2001).

More recently, specialists in HIV/AIDS are experiencing a growing number of HIV-infected persons asking for advise regarding natural pregnancy (Chen et al., 2001), some of the above mentioned arguments being an explanation for this trend. Furthermore, natural conception is frequently pursued in couples following assisted reproduction programmes. In one Italian study, up to one-third of couples did not start the insemination process and another third withdrew after a number of failed attempts. Half of couples failing ART in a Milan center attempted natural conception by practicing unprotected sex without medical control (Vernazza et al., 2006).

Aware of these conflicts, it is crucial that medical advice is offered before reproductive attempts of any nature are made by the uninformed patient (Barreiro et al., 2006a). As it is the case for other chronic illnesses, clinicians caring for HIV-infected patients under HAART should be ready to discuss issues regarding reproductive health and family planning whenever requested (Riley et al., 2005). Reproductive health in HIV has been recognized as a priority by the World Health Organization (2006) and by the US Department of Health and Human Services (2006). It is stated that HIV-infected individuals ‘should be able to have a satisfying, responsible and safe sex life, and that they should be able to reproduce and freely decide whether, when and how often to do so’. When taking care of HIV-serodiscordant couples, healthcare professionals should provide reproductive counselling, taking into consideration the following aspects: (i) need to minimize the risk of transmission to the uninfected partner and/or offspring; (ii) enabling informed reproductive choices; (iii) informing couples about the risks of HIV transmission and chances of pregnancy, in both natural and medically assisted conception; (iv) preparing couples for the psychological impact of assisted conception (availability, duration of treatment, failure and logistics); (v) discussing the possibility of foster or adoptive parenting and (vi) informing and advising couples about the risks of sexual and vertical transmission of other frequently associated agents, such as hepatitis B or C viruses.

Reproductive counselling

In keeping with these recommendations, and in the context of reproductive advice, we have proposed that any HIV-serodiscordant couple planning pregnancy should be evaluated in a standardized manner (see Table 1) (Barreiro et al., 2006a). First, a personal interview with both members of the couple should assess their current understanding of HIV, especially of those aspects related with reproduction, transmission and survival. Among the many issues to be considered at front, the status of HIV infection of the partner is the most important, given that the risk of viral transmission following conception
Table 1: Proposed protocol to evaluate HIV-serodiscordant couples wanting to be parents

<table>
<thead>
<tr>
<th>General discussion with the couple</th>
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<tr>
<td>Risk of HIV transmission, and other infections (hepatitis B or C), to seronegative partner and/or newborn</td>
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Factors affecting transmission
- HIV-RNA and CD4+ cells count
- Genital tract: infections, dysbacteriosis, inflammation, dysplasia, erosions, etc. (both members of the couple)
- Tobacco, alcohol and illicit drugs

Stability and duration of couple relationship

Life expectancy of HIV-positive partner

Age of the mother: risk for birth defects and reduced fertility

Fertility impairment due to HIV infection and/or antiretrovirals

Adverse outcome of pregnancy or teratogenicity due to antiretrovirals

Reproductive options
- Natural conception
- Self-insemination
- Assisted reproduction
- Other options
  - Adoption
  - Accepting no children

Clinical evaluation of each partner

History: special attention to
- HIV status: opportunistic events, CD4 count, viral load
- Antiretrovirals: adherence, tolerance, experienced in pregnancy, teratogenicity
- Fertility: menstrual cycles, infertility factors

General examination

Pelvic exam: bacterial vaginosis, cervical dysplasia

Investigations

- Hematology and biochemistry: Blood type
- Screening for: HIV, Hepatitis A, B and C, Cytomegalovirus, Herpes simplex, Rubella, Toxoplasma and Syphilis

Culture of genital secretions: Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis, etc.

Vaccination status: consider rubella, varicella, hepatitis A/B

Evaluation of fertile potential (specially indicated if history of AIDS, urologic/gynecologic complications or advanced age)

Male partner: spermiogram (count, motility, morphology)

Female partner
- Thyroid hormones
- LH, FSH, estradiol, progesterone and prolactin
- Pelvic ultrasound
- Hysterosalpingogram (if recommended according to past history)

Attempts is directly correlated to the level of plasma viremia. Gray et al. (2001) showed lack of sexual HIV transmission through unprotected intercourse in couples in which males had viral load values <1500 HIV-RNA copies/ml. The long-term follow-up of a Spanish HIV-serodiscordant cohort has shown a sharp decline in the incidence of HIV infection since the beginning of the HAART era in 1996 (Castilla et al., 2005). In fact, among a total of 393 couples examined, there were no single instances of HIV seroconversion in the 60 couples in which the infected partner was under HAART.

The attainment of suppressed HIV replication in blood is highly associated with undetectable HIV-RNA in seminal plasma (Zhang et al., 1998; Kim et al., 1999; Gupta et al., 2000; Bujan et al., 2002). However, some reports have shown that, despite absence of free virions in semen, it is possible to detect cell-associated HIV. The clinical significance of these findings is unknown for the moment, and the detection of integrated HIV-DNA in semen cells does not necessarily reflect the presence of infective virions (van Leeuwen et al., 2007).

Certain studies have shown that HIV-RNA may be amplified in semen, when undetectable in plasma, in 2–8% of patients under HAART (Vernazza et al., 2000; Bujan et al., 2004a). For some authors these findings indicate that the genital tract may represent a separate reservoir for viral replication (Nunnari et al., 2002), mainly due to reduced penetration of some antiretrovirals (Taylor et al., 2001); for others it could reflect the intermittent passage of HIV-infected lymphocytes from the vascular to the genital compartment (Leruez-Ville et al., 2002). Episodes of discordance in the detection of HIV-RNA in blood and sexual fluids may be in part explained by the use of suboptimal therapy, such as regimens with unboosted protease inhibitors (Barroso et al., 2000; Vernazza et al., 2000), due to low CD4 counts, or if inflammatory infiltrate is present in semen (Bujan et al., 2004a). It may also take >6 months under effective HAART for HIV replication to be completely suppressed in sexual secretions (Barroso et al., 2000).

Genital tract infections take into account for a significant number of episodes of HIV genital shedding (Reichelderfer et al., 2000). Importantly, eradication of genital tract pathogens is followed by a reduction in the HIV concentration in genital fluids (Rotchford et al., 2000). These data strongly suggest that sexual transmitted infections and inflammatory conditions are to be discarded and, if recognized, treated before the couple engages in any reproductive process. The use of regimens including drugs with good penetration through the hematogenital barrier (i.e. zidovudine, lamivudine, abacavir, tenofovir, nevirapine or protease inhibitors with ritonavir boosting) is also advisable.
When the woman is the one infected, even in the best circumstances (mother receiving HAART, having undetectable viremia, high CD4 counts, perinatal prophylaxis with antiretrovirals, etc.), there is still a residual risk of giving birth to an infected child (European Collaborative Study 2001; Cooper et al., 2002; Thorne and Newell, 2005). This risk is independent of the pregnancy being achieved by artificial or natural means and, according to the largest series in the HAART era, it is now around 1–2% in developed countries (Sperling et al., 1996; Burns et al., 1997; European Collaborative Study, 1999). It is likely that the chances for materno-fetal HIV transmission would be lower in the particular case of well-controlled women with complete viral suppression throughout the entire period of pregnancy. HIV-infected women should also know about the potential risks of in utero exposure to antiretroviral medications, which may affect the outcome of pregnancy (European Collaborative Study, 2003; Tuomala et al., 2002, 2005; Watts et al., 2004) or the health of the newborn (Anonymous, 2000, 2005; Barret et al., 2003; European Collaborative Study, 2003).

The fertile potential needs to be assessed before HIV-infected individuals engage in conception attempts. It is well established that HIV infection may impair sperm parameters, low CD4 cell counts being the main determinant (Nicopoulos et al., 2004). In the case of HIV-positive women, either the virus or antiretroviral medications seem to be responsible for lower pregnancy rates as compared with age-matched healthy controls (Coll et al., 2006). The age of the woman, particularly when above 35 years, is an important variable that affects fertility and should be taken into consideration also. Given its simplicity, all male partners should have a spermogram evaluation before checking reproductive options. Basic hormonal tests, pelvic ultrasound and, if recommended based on prior history, hysterosalpingography should be performed in female partners. If fertility problems are encountered natural pregnancy should be discouraged, leaving ART as the main alternative.

Natural pregnancy

As a crucial point in reproductive counselling, HIV-serodiscordant couples should be informed of all reproductive options available. The discussion needs to include their feelings about natural conception, assisted reproduction, adoption or even the acceptance of not having children. The very low risk of HIV transmission to the negative partner and to the baby if HIV-positive individuals have undetectable viremia under HAART is the basis for accepting natural pregnancy as an alternative option, while this possibility should be strongly discouraged outside these two sine qua non criteria. In the case of HIV-positive men, the demonstration of negative HIV-RNA in semen may be valuable information, since correlates well with lack of HIV transmission. There are no comparison data on the safety and efficacy of assisted reproduction versus natural conception under effective HAART in HIV infected individuals. The couple should also know that there is much ample controlled experience with ‘sperm washing’ procedures, as natural conception is still registered in small series (Barreiro et al., 2006b). From our point of view ‘sperm washing’ is the only alternative for HIV-infected men in whom undetectable viremia is unattainable due to antiretroviral drug resistance.

Restriction of unprotected sexual intercourse to woman’s fertile days is of major importance to minimize the risk of HIV transmission and to maximize the chances of natural pregnancy. Attempts of natural pregnancy should not be done for >6–12 pinpointed ovulations; if pregnancy has not been achieved along this period the couple should be considered for further fertility studies and assisted reproduction.

The outcome of natural pregnancies in HIV-serodiscordant couples receiving conceptional advise in three Spanish HIV clinics has recently been published (Barreiro et al., 2006b). In this report, all HIV-infected persons had undetectable plasma viremia under HAART for >6 months before attempting natural pregnancy. A total of 62 HIV-serodiscordant couples attained natural pregnancies. In 22 instances the female partner was HIV-positive and in 40 it was the male partner. Overall, 76 natural pregnancies occurred and 68 children were born. There were no cases of HIV seroconversion in uninfected partners. Unfortunately, one newborn acquired vertical HIV transmission. Of note, 55% of women and 75% of men had chronic hepatitis C, and there were no cases of sexual or vertical HCV transmission. This small experience should be taken for the moment as the proof-of-concept that risk of HIV transmission can be minimized, but never eliminated, in couples seeking a baby by natural means. Given that the average risk for heterosexual HIV transmission has been estimated to be 0.001–0.0001 per sexual contact (Gray et al., 2001) in theory, a series of 3000–30 000 natural pregnancies would be needed to truly establish the safety of such an approach (Englert et al., 2004).

It is clear, however, that experience with natural conception outside the framework of effective HAART, and confirmed undetectable HIV-RNA in plasma, has not been satisfactory and should be strongly discouraged. Thus, Mandelbrot et al. (1997) found a 4.3% rate of seroconversion in 92 HIV-negative women attaining natural pregnancy with their HIV-positive partners, of whom only 21% were under antiretrovirals. A survey in an Italian center showed that nearly half of the 500 HIV-discordant couples evaluated for assisted reproduction attempted at natural conception on their own, one HIV seroconversion being registered among them (Vernazza et al., 2006). The authors views coincide with our own in underscoring the importance of expert reproductive counselling before reproductive attempts are initiated.

Ethical issues

Reproductive counselling in HIV-serodiscordant couples raises important ethical questions (Englert et al., 2001; Baker et al., 2003; Spriggs and Charles, 2003; Ethics Committee of the American Society for Reproductive Medicine, 2004; Shenfield et al., 2004), as vertical and, to a much lesser extent, sexual HIV transmission can never be absolutely ruled out. The ethical dilemma regarding HIV perinatal infection is similar in some aspects to that of couples carrying autosomal recessive
diseases (i.e. Tay-Sachs disease, sickle-cell anaemia and cystic fibrosis) with the difference that in these conditions the chances for fetal inherited disease may be as high as 25%, while it is <2% for HIV-infected mothers when she and the newborn receive adequate care. Balancing the risks of HIV infection with the benefits of parenthood should be considered as ethically acceptable if couples and doctors take all reasonable precautions to prevent transmission, and the parents are prepared to take care of children regardless of its medical condition (Ethics Committee of the American Society for Reproductive Medicine, 2004).

With respect to sexual transmission of HIV, the epidemiologic evidence is limited but suggests a very low risk, although never absent, when HIV load is optimally suppressed with HAART. Sporadic reports of HIV horizontal transmission have followed both natural and assisted conception attempts. Ideally, practitioners should explicitly discuss available data on the safety of assisted reproduction or natural conception, and the effectiveness of proposed risk-reduction strategies. Any reproductive attempt should never be done before a standardized evaluation of the HIV-serodiscordant couple, the work-up proposed being one possible option (Table 1). Within this strict framework, health professionals taking care of HIV-infected persons who wish to be parents may play a crucial role in further reducing the risks of HIV transmission, and increasing the chances of attaining pregnancy under the best safety conditions.

Finally, it should be recognized that the debate between natural means or assisted reproduction for attaining pregnancy is at the present moment irrelevant for many HIV-serodiscordant couples. The improvement in the clinical status of HIV-infected individuals provided by HAART, together with some limitations of ART, has led many HIV-infected persons considering, if not trying at their own, to be parents by natural means (Englert et al., 2001). These facts should encourage HIV doctors to provide reproductive counselling to their patients, with the main objective of reducing the chances of HIV transmission and allowing couples to fulfill personal reproductive goals (Greco et al., 1999; Spriggs and Charles, 2003).

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