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REPRODUCTIVE MEDICINE

Consultations of HIV-infected women who wish to become pregnant

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Abstract
Purpose The aim of this study was to determine the impact and outcome of consultations of HIV-infected women if a pregnancy is planned.
Methods This study was performed retrospectively based on patient's records of HIV-infected women with the desire to become pregnant between 2000 and 2008. Relevant data regarding HIV infection, obstetrical history, diagnostic procedures and medical interventions related to conception, as well as pregnancy outcomes, were evaluated.
Results A total of 57 HIV-infected women (and their partner) were included; 38% ($n = 22$) of the couples showed a reduced fertility and 24 women (42%) became pregnant once or several times during the study period. Conception resulted from unprotected intercourse ($n = 11$), self-insemination ($n = 10$), assisted insemination ($n = 2$) or in vitro fertilization ($n = 1$). The outcome of all pregnancies was: 26 live births, 1 intrauterine fetal demise (38 weeks), 1 miscarriage, 1 cervical pregnancy and 1 legal abortion. No horizontal transmission occurred in serodiscordant couples. Seven (12%) women were lost to follow-up, 12 couples (21%) abandoned the attempt to get pregnant, and 14 couples (25%) reported an ongoing wish for a child.
Conclusions In this group of HIV-affected couples, we showed a high rate of reduced fertility. In our study, consultations and interventions led to a pregnancy rate of 42% without horizontal transmission of HIV.

Keywords HIV-1 · Pregnancy · Fertility · Consultation · Conception

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Introduction

Nearly half of all HIV-infected people living worldwide are women and most of them are in the reproductive phase of life (UNAIDS Report 2009) [1]. Despite their chronic disease, these women wish to have children as much as the general population [2, 3]. In developed countries, highly active antiretroviral therapy (HAART) has enabled HIV-infected people to live with an asymptomatic, chronic infection and achieve a good life quality and expectancy. However, several specific questions arise when HIV-positive women plan to conceive. Most importantly, unprotected intercourse bears the risk of horizontal transmission of HIV in serodiscordant couples. Also, HIV-infected women fear transmitting HIV to their baby during pregnancy or birth, as well as harm the fetus by taking antiretroviral medication. Mother-to-child transmission (MTCT) of HIV can be reduced with adequate measures to very low levels (<1%) [4]. Nevertheless, even if recent data from the Antiretroviral Pregnancy Registry [5] show no increase in birth defects when compared to the general population, it is still possible that exposure to ART has an impact on the future life of the offspring and may, for example, be carcinogenic. Reduced fertility related to chronic HIV

infection [6, 7] might also be a problem. Even though there is a growing acceptance of the right of HIV-affected couples to have children, some problems remain. In Germany, most fertility centers do not offer treatment to HIV-infected women, mainly because of concerns about ethical and legal issues, safety of procedures and HIV exposure of health-care employees. Most HIV-affected couples conceive without prior consultation at a specialized center or with an HIV-experienced gynecologist [3]. Unprotected intercourse with the aim of becoming pregnant is practiced even more frequently by those women taking HAART, who ideally achieve full suppression of their viral load [8]. In our study, we sought to determine the issues HIV-infected women are confronted with when they plan to get pregnant, the content of preconception consultations, possible medical interventions and their outcome.

Materials and methods

The patient records of HIV-1 infected women who attended our specialized outpatient center for gynecologic and obstetrical problems between the beginning of 2000 and the end of 2008 were evaluated retrospectively. All HIV-1 infected women who came for consultation because of their desire to have a child were included in this analysis. Patient history at our outpatient clinic was routinely taken using a standardized questionnaire. The following parameters were documented: country of origin, age, HIV status of the partner, as well as relevant data about the women's HIV infection [CDC classification, AIDS-related diseases, date of diagnosis of HIV infection, most likely route of HIV infection, current CD4 count and viral load as well as antiretroviral therapy (ART)]. Regarding the wish for a child, we documented the duration of attempts to conceive, all methods the couples had previously tried, and prior pregnancies and their outcome. All medical interventions after the first consultation in our clinic (such as diagnostic tests, reproductive technologies), as well as all conceived pregnancies and their outcome, were evaluated. Recommendations were given depending on the individual situation of the couples (see flowchart in Fig. 1): Discordant and concordant couples with a normal or only a slight reduction of their fertility were advised to practice self-insemination (in case of discordance) or unprotected intercourse (in case of concordance). Timing of the conception period was optimized by using LH-ovulation tests. Since 2008 [9], discordant couples with a fully suppressed viral load of the HIV-infected women under HAART were informed about the possibility of unprotected intercourse at the time of

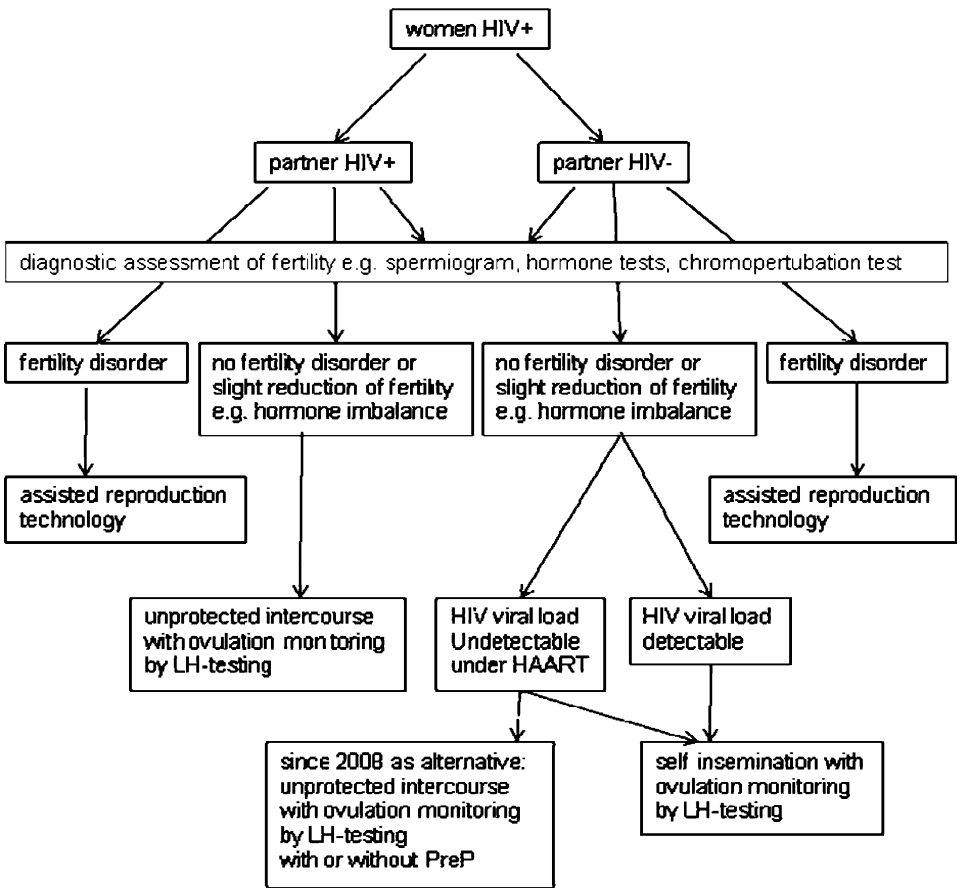

Fig. 1 Counseling of HIV-affected couples

ovulation with or without an antiretroviral pre-exposure prophylaxis of the HIV-uninfected partner. All couples with a significantly reduced fertility were referred to fertility treatment such as in vitro fertilization. All recommendations were made according to the current German–Austrian guidelines and former versions [10]. Descriptive analysis of the recorded data was performed to detect and address problems and needs of HIV-infected women who plan to get pregnant and to illustrate the outcome of our consultation.

Results

A total of 57 HIV-infected women were eligible in the study period according to the above-mentioned inclusion criteria; 39 of these women (68.4%) had HIV-negative partners and 18 of the male partners were HIV infected. The demographic and HIV-related data of this cohort are shown in Table 1. Of the female participants of this study, 66.7% (38/57) were taking antiretroviral medication at their first consultation, with a total of 24 different antiretroviral regimens. Assuming that most women from high prevalence countries (particularly Sub-Saharan Africa) have been infected with HIV by heterosexual contacts, the majority (96%) of this study population had a heterosexual infection risk (Table 1). Of the women, 38 had had one or more previous pregnancies. These resulted in 26 live births (15 women with one child, 4 with two and 1 with three children). Four women reported having undergone a legal abortion because of their HIV infection.

The mean duration of the couples' current wish to get pregnant was 2.4 years (range 1–10 years). As much as 18 women had tried to conceive by unprotected intercourse (6 of them with a discordant partner), 12 by self-insemination and 2 by in vitro fertilization in the past; 25 women had not tried to become pregnant before the consultation. More than a third of the women (22/57, 38.6%) reported having had unprotected intercourse at any time or regularly since receiving their diagnosis of HIV infection.

On average, the study participants presented 5.5 times (range 1–13 visits) to our outpatient clinic for counseling, diagnostic investigation or fertility treatment.

In the study period, 24 of the 57 women (42%) became pregnant with a total of 30 pregnancies. These pregnancies resulted in 26 live births, 1 stillbirth, 1 miscarriage, 1 cervical gravidity and 1 abortion. A first-trimester legal abortion was carried out because of newly emerged psychosocial problems. A total of 3 women conceived during the first three menstrual cycles after the initial consultation, another 7 participants within 12 cycles and in 14 couples more than 12 cycles were needed. The mode of conception of the first pregnancy of these 24 couples is presented in Table 1.

Table 1 Demographics

HIV-1 infected women ($n = 57$)	
Origin (n)	
Germany	14
Central Europe	3
Africa	38
Asia	2
Age (mean years, range)	32.6 (25–43)
Risk of HIV infection (%)	
Heterosexual contact	30
Origin from a high prevalence country	66
Blood transfusion	2
Unclear	2
Years since diagnosis of HIV infection (mean years, range)	6.5 (1–16)
CDC classification (n)	
A	32
B	16
C	5
ND	4
Current CD4 count (mean cells/μl, range)	453 (50–1,162)
Nadir CD4 count <200 cells/μl (n)	10
Viral load (mean copies/ml, range)	12.781 (836–122.000)
Not detectable (<50 copies/ml) (n)	44
Taking antiretroviral therapy (ART) (n)	38
NRTI alone (n)	5
NNRTI based (n)	12
PI based (n)	19
PI and NNRTI (n)	1
Integrase inhibitor (n)	1
Time on ART (mean years, range)	4.6 (1–10)
Mode of conception of first pregnancy ($n = 24$) (n)	
Unprotected intercourse	11
Self-insemination	10
Assisted insemination	2
In vitro fertilization	1

Reduced fertility was found in 22 (38.6%) of the 57 couples. In this subgroup of couples with fertility disorders, the overall pregnancy rate was 36.4% (8/22). The causes of fertility disorders, recommended measures for conception and outcomes of different subgroups are shown in Table 2.

In 4 of the 11 couples who conceived by unprotected intercourse, the male partner was known to be HIV negative. All four women of those couples were receiving HAART at the time of conception and had a fully suppressed viral load. All serodiscordant partners were tested after conception occurred, and no horizontal transmission

Table 2 Causes of reduced fertility, recommended measures and outcomes of different subgroups

	Male HIV−/ fertility+ ($n = 23$)	Male HIV−/ fertility− ($n = 16$)	Male HIV+/ fertility+ ($n = 12$)	Male HIV+/ fertility− ($n = 6$)
Causes of reduced fertility (n)				
Only women affected				
Tubal occlusion	–	5	–	1
Uterine abnormalities	–	6	–	1
Hormonal disorder	–	–	–	1
Only man affected				
Oligospermia	–	1	–	–
Asthenospermia	–	2	–	–
Both partners affected				
Tubal occlusion + oligo/asthenospermia	–	2	–	1
Uterine abnormality + oligo/asthenospermia	–	–	–	2
Recommended measures				
Unprotected intercourse	6	1	12	3
Self-insemination	17	7	–	–
Assisted insemination	–	2	–	1
IVF or ICSI	–	6	–	2
Additional intervention (e.g., myomenucleation)	–	6	–	2
At least one pregnancy occurred (n)	11	5	5	3
Mode of conception (n)				
Unprotected intercourse	3	1	5	2
Self-insemination	8	2	–	–
Assisted insemination	–	2	–	–
IVF	–	–	–	1

was seen. Furthermore, there was no MTCT during the study period.

In the group where no pregnancy occurred ($n = 33$), 12 couples abandoned their attempts to conceive for the following reasons: age over 40 years ($n = 7$), hysterectomy ($n = 3$), separation from partner ($n = 1$) and psychiatric illness ($n = 1$). While 14 couples (25%) reported an ongoing wish for a child, 7 (12%) were lost to follow-up.

Discussion

Fear of transmission of HIV to a future child or an HIV-negative partner and infertility are the main reasons of couples with a known HIV infection in one or both partners to seek reproductive counseling in a specialized clinic. The pregnancy rate achieved in the couples seen in our clinic was 42% after individual consultation, specific diagnostic testing and in some cases fertility treatment. Several points had a major influence on the outcome of attempts to conceive. Firstly, we assume that this was a highly preselected group, as the majority of HIV-affected couples get pregnant without prior specific counseling [3], and the desire to have a child in our cohort had been ongoing for a considerable period of time (mean 2.4 years). In view of this, the number of pregnancies achieved so far is encouraging even if the study results are limited because of the small sample size and the retrospective design.

Furthermore, we found a significant number of patients with decreased fertility. A high rate of infertility in HIV-infected women is reported in literature [6, 7]. Some of the reasons for infertility or subfertility in these women are tubal occlusion in consequence of more severe and more frequent ascending genital infections [6, 11] and HIV infection per se (mainly due to hormonal disorders in women with advanced disease and low CD4 count) [12]. Because of the high rate of cervical intraepithelial lesions, cervical factors due to procedures such as cone biopsies also play a role [13]. A long duration of HIV infection, the severity of their immune defect or HIV disease may therefore also decrease fertility in these women. In our cohort, the mean time since the diagnosis of HIV infection was 6.5 years. Even though the current immunological status in most of the participants was satisfactory with a mean CD4 count of 453 cells/µl, almost half of them had had clinical symptoms of their HIV infections and/or a

CD4 nadir of less than 200 cells/μl in the past, making them more vulnerable to genital infections. Other factors, such as uterine fibroids, might have been more predominant in our cohort because of the relatively high percentage of patients with African ethnicity (36%) [14].

In addition, all except one of our subjects received an antiretroviral regimen including a nucleoside reverse transcriptase inhibitor (NRTI). NRTIs are known to cause mitochondrial toxicity [15]. A recent study showed that there is a depletion of mitochondria in oocytes of women receiving ART, therefore reducing their fertility [16].

HIV-positive women with a known fertility disorder face additional obstacles: It may still be difficult for them to find a specialized center willing to provide care for couples with HIV, and the outcome of assisted reproductive interventions seems to be less promising [17]. In our subgroup of 22 couples with a proven fertility disorder, only eight pregnancies could be achieved, three of these by assisted reproduction.

Most couples without fertility issues rarely attend a specialized care center except for counseling about methods of conception if the partner is serodiscordant. This confirms the findings by other authors [3]. For serodiscordant couples with HIV infection in the female partner, using condoms with subsequent self-insemination (with or without ovulation prediction) is an easy, cheap and readily available option, and should be the method of choice [18]. However, personal or cultural reasons might render this option unacceptable for some couples [19]. For these couples, unprotected intercourse at the time of ovulation can be discussed if the infected partner is receiving HAART, the viral load is fully suppressed and there is no evidence of other sexually transmitted diseases [9]. Under these conditions, Barreiro et al. [20] reported 72 pregnancies in 62 couples. No horizontal transmission occurred, but one child was infected vertically. Even if the transmission risk to the partner seems to be very small under these optimized circumstances, the couples need to be informed accordingly [20, 21]. Whether adding an antiretroviral "pre-exposure prophylaxis" (e.g., Tenofovir) at the time of planned intercourse further decreases the risk to the uninfected partner remains unclear, as reliable data have not yet been published [22, 23].

In conclusion, our data show that HIV-affected couples who wish to become pregnant have an urgent need for appropriate consultation addressing their individual requirements and elucidating their treatment options. Even if some couples may abandon their wish to conceive, the overall rate of pregnancies after appropriate counseling and testing is encouraging.

Conflict of interest We declare that we have no conflict of interest.

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