Article

Assessing the treatment efficacy of IVF with intracytoplasmic sperm injection in human immunodeficiency virus-1 (HIV-1) serodiscordant couples

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Abstract

The purpose of this study was to evaluate the treatment efficacy of using IVF–intracytoplasmic sperm injection (ICSI) in HIV serodiscordant couples interested in having children while minimizing the risk of viral transmission. This study reviews the cases of HIV serodiscordant couples (n = 142) seeking fertility treatment at an assisted reproductive centre. The main outcome measures were successful pregnancy rate and HIV seroconversion rate. In calculating crude pregnancy rates, only patients who were actually treated were taken into account. To compensate for cancelled patients, and patient drop-out, life-table analysis was performed. Life-table analysis demonstrated that 37.0 ± 5.0% of couples attain a successful pregnancy after one completed IVF–ICSI with embryo transfer (IVF–embryo transfer) cycle. Following two and three IVF–embryo transfer cycles, the pregnancy rates rose to 56.8 ± 6.0 and 73.4 ± 6.9% respectively. Overall pregnancy rates were inversely related to age. There were no HIV seroconversions in treated patients or in delivered babies. It is concluded that the use of IVF–ICSI to avoid disease transmission in HIV-1 serodiscordant couples desiring children appears to be safe and yields high rates of pregnancy. However, success is influenced by the woman's age.

Keywords: *fertility, HIV-1, ICSI, IVF, life-table analysis, pregnancy rate*

Introduction

Human immunodeficiency virus (HIV) infection is common worldwide. Today, 40 million people are estimated to be living with HIV; of these, 37 million are adults. An estimated 5 million people acquired HIV in 2003, including 4.2 million adults (UNAIDS, 2003). Although the length of time from initial infection to development of clinical disease varies widely, the median time for untreated patients is approximately 10 years. The advent of highly effective antiretroviral therapy has significantly improved survival expectations (Anonymous, 2000; Tam *et al*., 2002; Morris *et al*., 2003). The improvement in quality of life and the increase in survival of individuals with HIV have given many the hope of living a normal life, which includes starting a family.

Most HIV infections occur in individuals of reproductive age, and heterosexual contact remains the most common route of infection in women. As a result, sexually active couples in which one or both partners are seropositive are advised to use condoms to prevent viral transmission through the exchange of reproductive body fluids or blood. In couples desiring children, various techniques have been suggested to eliminate or greatly lessen the transmission risk of virus from seropositive men. Both intrauterine insemination (IUI) and IVF with intracytoplasmic sperm injection (IVF–ICSI) have

been utilized to help couples achieve pregnancy while minimizing the risk of seroconversion (Semprini *et al*., 1992; Jamieson *et al*., 2001; Ohl *et al*., 2003).

In Europe, assisted reproductive technology clinics have been providing fertility care to HIV-1-infected couples for many years (Politch and Anderson, 2002). Most practitioners of assisted reproduction in the United States are reluctant to treat men seropositive for HIV. Although the Centre for Disease Control (CDC) recommends against treatment with IUI, the American College of Obstetricians and Gynecologists (ACOG) and the American Society of Reproductive Medicine (ASRM) have issued statements endorsing a policy of non-discrimination for couples seeking assistance (ACOG Committee on Ethics, 2001; Ethics Committee of the ASRM, 2002).

Since 1998, Columbia University has accepted men seropositive for HIV-1 for reproductive care using IVF–ICSI (Sauer and Chang, 2002; Pena *et al*., 2003). This reproductive choice is provided in the hope of preventing horizontal and vertical transmission of virus to the partners and children of these men. The purpose of this study is to evaluate the efficacy of IVF–ICSI in HIV serodiscordant couples by examining the relationship between the number of cycles and successful pregnancy outcomes.

Materials and methods

The original protocol for providing assisted reproduction to HIV serodiscordant couples using IVF–ICSI was reviewed and approved by the Institutional Review Board and Ethics Committee of Columbia University, New York, NY (Sauer and Chang, 2002). Between July 1997 and April 2004, 142 HIV-1 serodiscordant couples in which the male partner was HIV-1 seropositive and the female partner was seronegative were screened for fertility treatment; of these, 108 (76%) were deemed suitable for treatment. Patients included in the study were from all social and ethnic groups. Details of the protocol and procedures used in treating these couples have been previously described (Sauer and Chang, 2002). The technique for separating spermatozoa from virus involves removing HIV-infected leukocytes and macrophages in the semen from the most motile spermatozoa by gradient centrifugation in combination with 'swim-up'. Semen is handled by trained embryologists in a class II biological safety cabinet. Semen used for ICSI was processed by centrifuging it through a discontinuous density gradient (Sage BioPharma, Bedminister, NJ, USA, PureCeption, cat. no. PAP U12 HTF and cat. no. PAP CL12) as follows: 1.5 ml of the lower (90%) layer was pipetted into one (or more, depending on semen volume) Falcon 35 2095 tubes; 1.5 ml of the upper (47%) layer was carefully pipetted on top of this, and 1–2 ml of semen was pipetted directly on top of the upper layer. The gradient tube(s) were centrifuged for 10–20 min at 300 *g*. Following this spin, the pellet(s) were transferred to a clean Falcon 35 2095 tube and diluted with 5 ml of modified HTF (Irvine Scientific, Santa Ana, CA, USA, cat. no. 9963) supplemented with 5% (v/v) HSA (Sage BioPharma, cat. no. ART-3001). The spermatozoa were centrifuged for a maximum of 10 min at 300 *g* and the supernatant (wash 1) was removed. The pellet was resuspended in 3 ml of fresh modified human tubal fluid-human serum albumin (HTF–HSA) and spun again for a maximum of 5 min. The supernatant (wash 2) was removed and the pellet was re-suspended in a small volume of modified HTF–HSA. Spermatozoa were then allowed a 45-min period for 'swim-up'. Only spermatozoa from the most motile fraction were then selected for ICSI.

A total of 156 IVF–ICSI cycles were analysed. Only those cycles which resulted in oocyte retrieval, fertilization with ICSI and embryo transfer (IVF–embryo transfer) were included in the analysis. Ten cycles were cancelled after retrieval and prior to embryo transfer due to either poor fertilization or embryo quality (n = 5) or risk of ovarian hyperstimulation syndrome (n = 5). This left a total of 92 couples who underwent 146 IVF–embryo transfer cycles. Female age and male age were recorded on the first day of each IVF–ICSI treatment cycle.

The main outcome measures were successful pregnancy rate and rate of HIV seroconversion. Successful pregnancy was defined as ongoing pregnancy or live birth. Ongoing pregnancy was defined as a viable pregnancy continuing beyond the first trimester. Pregnant women were followed by maternal–fetal medicine specialists in each trimester, and HIV-RNA-polymerase chain reaction (PCR) screens were performed every 3 months during the pregnancy. Infants and mothers were tested at birth and 3 months later by HIV-DNA-PCR, which is highly sensitive at detecting 10 or fewer copies of HIV-1 DNA per ml of whole blood DNA, or HIV-RNA-PCR, at 50 or fewer copies per ml. In non-pregnant patients, HIV-ELISA antibody screens were performed 3 months following embryo transfer.

Cumulative successful pregnancy rates were estimated by life-table analysis using the Kaplan–Meier product limit procedure (Kaplan and Meier, 1958). The basis for choosing the Kaplan–Meier estimator is the fact that survival function can best be expressed as a product of conditional probabilities, and that each observation, whether it is censored or uncensored, can help to estimate some of these conditional probabilities. In clinical trials, interest centres on an assessment of the time until participants experience a specific event (i.e. pregnancy in this study). Data that arise in this manner are termed survival data, and implicit in the definition of survival time is a well-defined start point. A unique feature of survival data is the presence of censored observations. Because of limited periods of follow-up in observational studies, only a portion of the survival time is observed for some participants. Thus, the data available for analysis will typically consist of some uncensored observations as well as some that are censored. Cumulative successful pregnancy rates were expressed as cumulative percentage probabilities with 95% confidence intervals (CI). Data were further stratified by age (under 34, 34 through 37, and 38 through 43 years). These computational procedures were run on SPSS for Windows version 11.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Ninety-two HIV serodiscordant couples underwent a total of 146 IVF–embryo transfer cycles, leading to 54 successful pregnancies. The mean age of the males was 37.1 ± 5.4 years (range 22–48 years), while that of the females was 33.4 ± 4.5 years (range 21–43 years). The average number of cycles per