Male reproduction and HIV-1 infection

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Intra uterine insemination with processed sperm for HIV serodiscordant couples in whom the man is HIV positive

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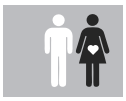
Abstract

The desire to have children is more and more common in HIV-serodiscordant couples. The Academic Medical Centre Amsterdam has developed a new treatment protocol for couples in whom the man is HIV positive. Semen is processed to obtain HIV-1-free spermatozoa. These spermatozoa are used for IUI treatment. Thus far, 20 serodiscordant couples underwent 76 IUI cycles. An insemination was performed in 50 cycles (66%). The insemination was cancelled in 26 cycles, because of too many follicles (risk for multiple pregnancy), weekend (no possibilities for virological testing), not enough spermatozoa after preparation, a positive HIV-1 RNA test and other reasons. 10 out of 20 women became pregnant (50%), 8 women were ongoing pregnant. The clinical and ongoing pregnancy rate per started cycle was 13% and 11% respectively. 7 babies have thus far been born and none of the mothers or babies seroconverted within this study period. Larger numbers of patients are necessary to support the safety of this program.



HIV-1 infection is a sexually transmitted disease that mostly affects men and women of reproductive age, of whom a growing number is heterosexual [1]. The introduction of highly active antiretroviral therapy (HAART) has led to an increase in life expectancy of HIV-1-infected men and women in the western world. As a result, many of these men and women have a desire to achieve parenthood. However, when a HIV negative woman has unprotected intercourse in order to become pregnant from her HIV-1-positive man, she is at risk of becoming HIV-1 infected herself, i.e. horizontal transmission.

The risk of horizontal transmission can be reduced drastically after processing of the semen to obtain an HIV-1-free fraction of spermatozoa, which can then be used for various kinds of artificial reproductive techniques. Semen processing is a four-step procedure: (1) centrifugation, (2) density centrifugation, (3) swim-up and (4) concentration. During semen processing the spermatozoa are separated from all other semen components, because the spermatozoa themselves are probably not HIV-1 infected. Until now this technique has been used abroad in more than 3000 treatment cycles leading to the birth of more than 500 children, without any seroconversion of the mother or child [2,3]

Since 2003, the Academic Medical Centre in Amsterdam offers intra uterine insemination (IUI) to HIV-1-serodiscordant couples with a HIV-1-positive man and a proven HIV-negative woman. The woman's age is limited to a maximum of forty years. Before the start of treatment the couple is informed extensively about the conditions on which HIV-IUI treatment is initiated. Couples are told that there is no 100% guarantee that infection with HIV-1 will not take place during treatment, that they should abstain from unprotected intercourse, and that the inseminations may not take place for various reasons. All patients must sign informed consent. Detailed information about the man's HIV-1 status and treatment is requested from the treating physician and all couples undergo a structured interview by a counsellor.

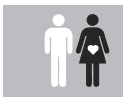
After the first visit a standardized fertility screen is performed to assess possible fertility problems. In addition, an HIV-1 semen processing is done to ascertain whether 3.5 million spermatozoa remain after processing, since this number is a prerequisite for treatment.

In a multidisciplinary team, where gynaecologists, embryologists, a counsellor, nurses, virologists and doctors from internal medicine are present, the decision whether or not to start treatment is taken.

During IUI treatment mild ovarian hyperstimulation takes place with recombinant follicle stimulating hormone (FSH). On the day of insemination the semen is produced in the morning, processed, and a part of the spermatozoa fraction is tested for the presence of HIV-1 RNA. The test, that has a positive and a negative internal control was validated in our own hospital and has a lower limit of detection of 10 HIV-1 RNA copies per portion of 2.5 million spermatozoa. Only when HIV-1 RNA tests in the spermatozoa fraction are negative, IUI is performed in the afternoon with the remaining part of the spermatozoa fraction. The woman undergoes HIV testing every three IUI cycles or at 4, 12 and 24 weeks gestation. The child undergoes an HIV test at the age of six months.

Until October 2004, twenty HIV-1-serodiscordant couples entered the IUI program after the initial screening. These twenty couples underwent 76 IUI cycles. In fifty cycles (66%) IUI was performed. In the other 26 cycles the insemination was cancelled: 11 times because of a risk of multiple pregnancy (more than two dominant follicles on trans-vaginal ultrasound), three times because the ovulation took place during the weekend (no possibility for virological testing), three times because the number of spermatozoa was too small after semen processing on the day of insemination, two times because the HIV-1 RNA test after processing was positive and seven times because of other reasons.

Ten women became pregnant (50%), eight of these women had an ongoing pregnancy. The percentage of clinical pregnancies, i.e. a pregnancy visible on ultrasound, and the percentage of ongoing pregnancies, i.e. a viable pregnancy on ultrasound at 12 weeks gestation, was 13% and 11%, respectively, per IUI cycle, and 20% and 16%, respectively, per insemination.



So far seven children have been born. Within this observation period, no seroconversions of the mothers or their offspring have been observed. Thus far, the results of this protocol are encouraging, but larger numbers of patients will be necessary to prove the safety of this treatment.

References

(1) Gras LAJ, van Sighem AI, van Valkengoed IGM, de Wolf F, for the Dutch Collaborative HIV treatment Centres. Monitoring of human immunodeficiency virus type 1 (HIV-1) in the Netherlands (Nov 2003). *Stichting HIV Monitoring, Amsterdam.* 2003.

(2) Sauer MV. Providing fertility care to those with HIV: time to re-examine healthcare policy. *Am J Bioeth.* 2003;3:33-40.

(3) Semprini AE, Levi-Setti P, Bozzo M, Ravizza M, Taglioretti A, Sulpizio P et al. Insemination of HIV-negative women with processed semen of HIV-positive partners. *Lancet.* 1992;340:1317-1319.

Appendix

Here we present an update of the data presented in Chapter 10 until December 2007.

Until December 2007, 50 HIV-1-discordant couples entered the IUI program after the initial screening (Table 1). These 50 couples underwent 233 IUI cycles. In 152 cycles (65%) IUI was performed, and in 81 cycles (35%) the insemination was cancelled. In 40 cycles the insemination was cancelled before the ovulation, because of a risk of multiple pregnancy (more than two dominant follicles on trans-vaginal ultrasound), an ovulation during the weekend (no possibility for virological testing) or for personal reasons. In 41 cycles the insemination was cancelled after the ovulation, because the number of spermatozoa was too small after semen processing on the day of insemination, the HIV-1 RNA test after processing was positive, the HIV-1 RNA test result was not reliable or because of other reasons.

Twenty-three women became pregnant (46%), 19 of these women had an ongoing pregnancy (38%) of whom 15 were singletons and 4 were twin pregnancies. The percentage of clinical pregnancies, i.e. a pregnancy visible on ultrasound, and the percentage of ongoing pregnancies, i.e. a viable pregnancy on ultrasound at 12 weeks gestation, was 11% and 8%, respectively, per IUI cycle, and 17% and 13%, respectively, per insemination.

The results of the IUI treatment are not constant over time, as is displayed in Table 1. A slightly higher number of couples underwent IUI in 2004, because the IUI treatment with processed semen for HIV-1-discordant couples with an HIV-1-infected man had been announced before the actual treatment was started in March 2003, and a virtual waiting list was created for couples who were interested in this specific treatment. People were called up from the waiting list as soon as the program was running. After the waiting list had been cleared, a low but steady number of couples applies for this treatment every year (Table 1).

The percentage of cancels varied from 22% to 44% during the first five years.

More than two follicles on gynaecological ultrasound during mild hyperstimulation with recombinant follicle-stimulating hormone (recFSH) was the most common cancel criterion during the first two years, but after we decided to lower the start dosage of recFSH in 2004, the percentage of cancels before ovulation decreased. From that year on, most cycles were cancelled after ovulation, with a poor semen quality after semen processing being the most common cancel criterion.

Table 1. Results of intra uterine inseminations with HIV-1 processed semen from 2003-2007

Variable	Outcome											
	2003		2004		2005		2006		2007		Total	
No. couples	13		21		18		13		15		50	
Age	34	(32-36)	31	(29-34)	31	(29-35)	32	(29-36)	35	(30-38)	32	(30-35)
No. cycles	33		65		46		43		46		233	
Cancel of cycles	13	(39)	20	(31)	19	(41)	19	(44)	10	(22)	81	(35)
No. follicles > 2, weekend or other reasons	10	(77)	13	(65)	6	(32)	8	(42)	3	(30)	40	(49)
TC< 2 M, test positive, invalid test	3	(23)	7	(35)	13	(68)	11	(58)	7	(70)	41	(51)
No. inseminations	20	(61)	45	(69)	27	(59)	24	(56)	36	(78)	152	(65)
IUI 1-3	20	(100)	28	(62)	18	(67)	16	(67)	14	(39)	96	(63)
IUI 4-6	0	(0)	14	(31)	5	(19)	8	(33)	10	(28)	37	(24)
IUI 7-9	0	(0)	3	(7)	4	(14)	0	(0)	12	(33)	19	(13)
Clinical pregnancies	5		8		6		3		4		26	
Miscarriage	0		1		1		2		2		6	
Ectopic pregnancy	0		1		0		0		0		1	
Ongoing pregnancies	5		6		5		1		2		19	(38)
Singletons	3		6		4		1		1		15	
Twins	2		0		1		0		1		4	
Babies born	7		6		6		1		3		23	
Pregnancy rates (%)												
Clinical pregnancies per cycle	15		12		13		7		9		11	
Clinical pregnancies per IUI	25		18		22		13		11		17	
Ongoing pregnancies per cycle	15		9		11		2		4		8	
Ongoing pregnancies per IUI	25		13		19		4		6		13	

Variables are expressed as median (interquartile range) or *n* (%) unless otherwise stated

The percentage of clinical and ongoing pregnancies was fairly good and steady during the first three years but in 2006 and 2007 pregnancy rates dropped (Fig. 1).

There are two possible explanations for the decreased pregnancy rates. First, in 2006, we started including men with lower semen qualities: During the first three years a total count after semen processing of 3.5 million spermatozoa were needed to enter the program, because 2.5 million spermatozoa were needed for PCR testing, and the remaining 1 million spermatozoa were left for insemination. From 2006 until 2007 only 1 million spermatozoa were necessary for PCR testing. Subsequently, a total count of only 2.0 million spermatozoa after semen processing was necessary to enter the program.

Second, the distribution of IUI cycles changed (Fig. 2). Discordant couples with an HIV-1-infected man do not practise unprotected intercourse because of an HIV-1-transmission

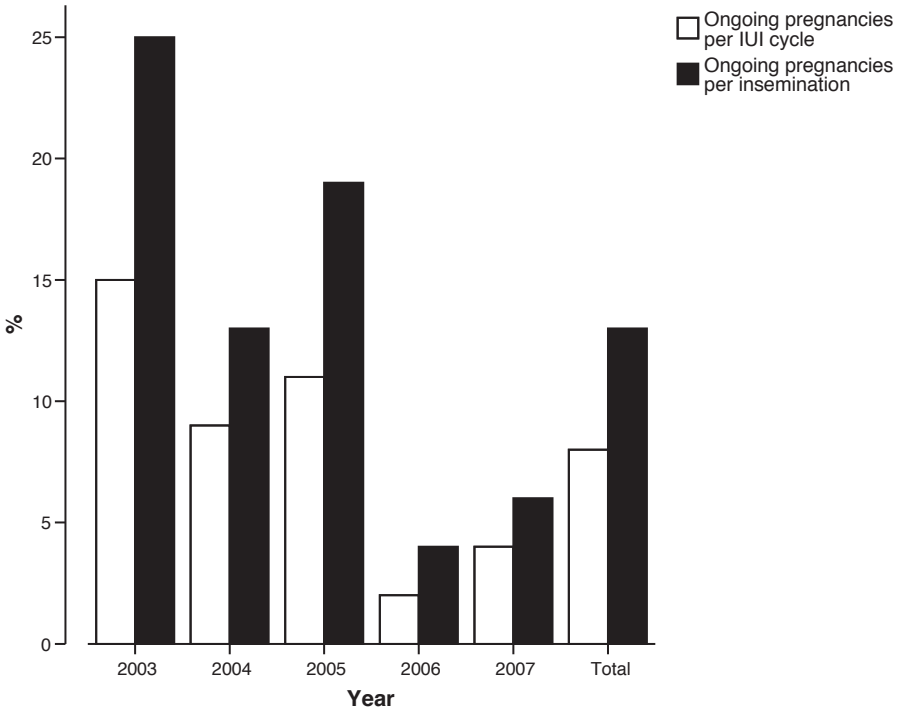


Figure 1. Ongoing pregnancies after IUI with HIV-1-processed semen

risk, as a consequence, and, analogous to women who undergo artificial insemination with donor semen, these couples are not infertile. In a normal infertile population 6–9 cycles of IUI are performed, and artificial cervical insemination with donor semen is performed for 12 cycles in our hospital. However, it is known that the first 2 cycles in conventional IUI and in donor insemination are more successful than the other cycles [4]. Unfortunately, these data did not exist for discordant couples with an HIV-1-infected man. In the light of the arguments mentioned above we decided to offer 9 cycles of IUI to these couples. Over the years the distribution of IUI cycles became more unfavourable and after IUI cycle 4, nobody ever became pregnant (Fig. 3).

Based upon these data we will now only offer 4 cycles of IUI, followed by IVF. We may also have to rethink the semen quality criteria, and perhaps, start with IVF sooner.

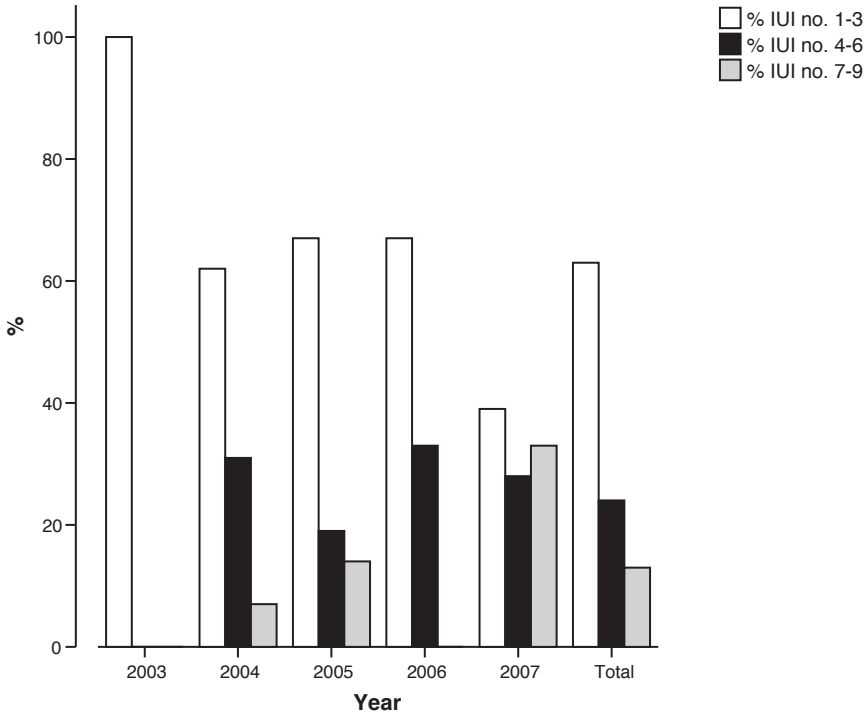


Figure 2. Distribution of IUI cycle numbers for first children

Nine couples returned for second children (Table 2). Five of them had an ongoing pregnancy (56%). The percentage of clinical pregnancies, and the percentage of ongoing pregnancies, was 19% and 16%, respectively, per IUI cycle, and 25% and 21%, respectively, per insemination. In these couples pregnancy rates were still good, unlike the couples that applied for first children (Fig. 4).

So far 28 children have been born. Within this observation period, no seroconversions of the mothers or their offspring have been observed. Still larger numbers of patients are necessary to prove the safety of this treatment.

Table 2. Results of intra uterine inseminations with HIV-1-processed semen for second children from 2005-2007

Variable	Outcome							
	2005		2006		2007		Total	
No. couples	1		3		7		9	
No. cycles	4		8		19		31	
Cancel of cycles	0	(0)	0	(0)	7	(37)	7	(23)
No. follicles > 2, weekend or other reasons					5		5	
TC< 2 M, test positive, invalid test					2		2	
No. inseminations	4	(100)	8	(100)	12	(63)	24	(77)
IUI 1-3	3	(75)	7	(88)	7	(58)	17	(71)
IUI 4-6	1	(25)	1	(12)	4	(33)	6	(25)
IUI 7-9	0	(0)	0	(0)	1	(9)	1	(4)
Clinical pregnancies	1		1		4		6	
Miscarriage	0		1		0		1	
Ectopic pregnancy	0		0		0		0	
Ongoing pregnancies	1	(100)	0	(0)	4	(57)	5	(56)
Singletons	1				4		5	
Twins	0				0		0	
Babies born	1				4		5	
Pregnancy rates								
Clinical pregnancies per cycle	25		13		21		19	
Clinical pregnancies per IUI	25		13		33		25	
Ongoing pregnancies per cycle	25		0		21		16	
Ongoing pregnancies per IUI	25		0		33		21	

Data are presented as *n* or %

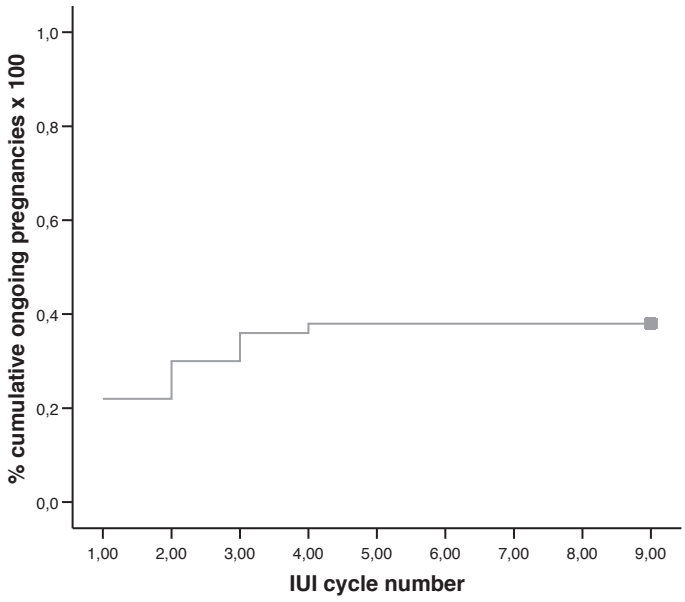


Figure 3. Cumulative ongoing pregnancies per IUI cycle

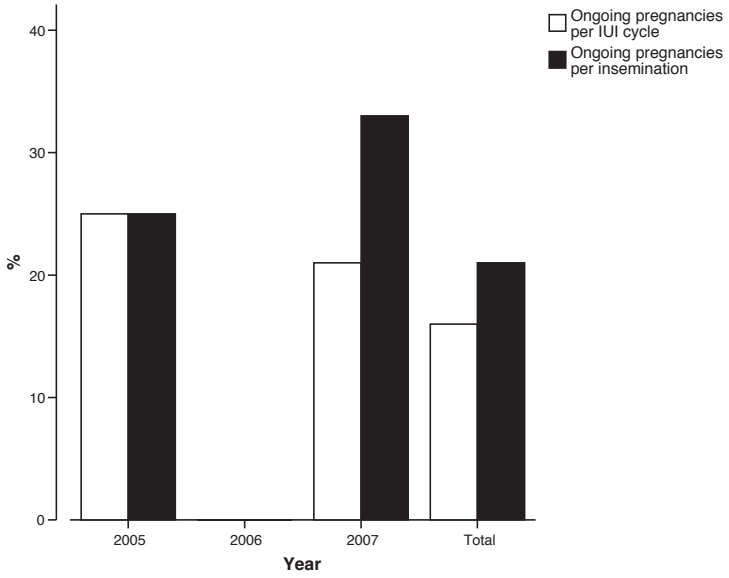


Figure 4. Ongoing pregnancies after IUI with HIV-1-processed semen for second children

References

(1) Custers IM, Steures P, Hompes P, Flierman P, van Kasteren Y, van Dop PA et al. Intrauterine insemination: how many cycles should we perform? *Hum Reprod.* 2008;23:885-888.