Women infected with human immunodeficiency virus type 1 have poorer assisted reproduction outcomes: a case-control study

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Objective: To compare the efficacy of assisted reproductive technology (ART) in women infected with human immunodeficiency virus type 1 (HIV-1) versus HIV-negative controls.
Design: Retrospective case-control study.
Setting: University hospital ART unit.
Patient(s): Eighty-two women infected with HIV-1 and 82 women as seronegative controls.
Intervention(s): Ovarian stimulation, oocytes retrieval, standard in vitro fertilization (IVF) or intracytoplasmic sperm injection, embryo transfer.
Main Outcome Measure(s): Clinical pregnancies and live-birth rates.
Result(s): After oocyte retrieval, all women infected with HIV-1 infected were matched 1:1 to HIV-negative controls according to the following criteria: date of ART attempt, age, parity, main cause of infertility, ART technique, and rank of attempt. Only the first IVF cycle during the study period was considered for each couple. We found no statistically significant differences between the two groups for ovarian stimulation data, fertilization rate, or average number of embryos transferred. The clinical pregnancy rate per transfer was statistically significantly lower for the cases compared with the controls (12% vs. 32%), as were the implantation rate (10% vs. 21%) and the live-birth rate (7% vs. 19%).
Conclusion(s): In one of the largest studies to pair six factors that influence the results of ART, HIV infection in women was associated with poorer outcomes after ART. These results suggest that women with controlled HIV-1-infection should be counseled not to

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delay ART in cases of self-insemination failure or other causes of infertility. Fertility preservation by vitrification of oocytes in women whose pregnancy should be delayed may be an important future consideration. (Fertil Steril® 2016;105:1193–201. ©2016 by American Society for Reproductive Medicine.)
Key Words: HIV-1, in vitro fertilization, assisted reproductive techniques, highly active antiretroviral therapy, case-control studies

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The human immunodeficiency virus (HIV) epidemic affects approximately 35 million people worldwide, and more than half are women (1). In France, nearly 150,000 people (95% confidence interval [CI], 134,700–164,900) were thought to be infected with HIV in 2010 (2), and the majority of the women living with HIV-1 are of reproductive age.

At present, 30 years after the discovery of HIV (3), the treatment and care of HIV patients have substantially improved. The introduction of highly active antiretroviral therapy (HAART) has increased the life expectancy of those affected and decreased the mother-to-child transmission from 15% to 20% for nontreated women to less than 1% (4–7). Moreover, pregnancy has little influence on the evolution of HIV disease, regardless of the CD4 count and viral load (8, 9). Consequently, persons living with HIV are expressing an increasing desire for children and are more frequently planning to procreate. For patients living with HIV, the desire for children should be addressed by a multidisciplinary team. The French and European guidelines for the medical care of people living with HIV-1 were recently updated, and early treatment is now recommended for all these patients (2, 10). Thus, an increasing number of women are conceiving while on HAART.

Nevertheless, unprotected sexual contact for procreation remains associated with a risk of transmission if the plasma viral load is not maintained at an undetectable level through long-term antiretroviral therapy (11, 12). It is necessary to recommend postponing conception in cases of current opportunistic infection, severe superimposed disease, or failure of virologic control. Depending on whether the woman or both partners are infected with HIV, the prevention of viral transmission within the couple and/or the treatment of infertility can lead to a couple requesting the use of assisted reproduction technology (ART). In cases of infertility of one or both members of a couple or in cases of failure of self-performed intravaginal insemination or timed intercourse ART is necessary. Reproductive techniques are selected and proposed based on the criteria used for the general population: (1) intrauterine insemination is used in cases of tubal patency and satisfactory sperm analysis, or (2) IVF, including standard techniques or intracytoplasmic sperm injection (ICSI), is used according to the degree of sperm alterations. Assisted reproduction technology is suggested for patients whose clinical health and fertility status allow it and in cases in which the general conditions for access to ART are met (13–15).

Many studies have investigated safe procreation for couples when the male partners is infected with HIV type 1 (HIV-1) (16, 17), but few studies have addressed infertility treatments for infected women. In women infected with HIV-1, mother-to-child transmission via the oocyte has never been demonstrated, so the risk of transmission after ART is similar to that observed in other women infected with HIV and depends on the plasma viral load and obstetric conditions. The disappointing pregnancy rates (18–26) have been suggested to be the result of a premature decrease in the ovarian reserve (27, 28), the impact of HAART on oocyte quality (29, 30), or the induction of inflammatory tubal factors by sexually transmitted coinfections (31, 32). In this context, we compared the outcomes of ART in women infected with HIV-1 with those obtained in healthy women as HIV-seronegative controls.

MATERIALS AND METHODS

Study Design

A retrospective, match-paired, case-control study of women attending the ART unit of Bichat-Claude Bernard University Hospital, Paris, France, was performed. As recommended by French bioethics laws, women infected with HIV-1 were evaluated by a multidisciplinary team. The team included ART physicians and embryologists, infectious disease specialists, virologists, obstetricians, pediatricians, and psychologists. We included all women infected with HIV-1 who underwent standard IVF or ICSI from January 1, 2009, to December 31, 2011.

Inclusion/exclusion Criteria

All couples in which the female partner was infected with HIV-1 were included, regardless of whether the male partner presented a concordant or different HIV serologic status. Couples in which the male partner was infected with hepatitis B (HBV) and hepatitis C (HCV) were not excluded.

Women infected with HIV-2 or coinfected with HBV or HCV were excluded to avoid confounding factors. Moreover, all of the patients who did not strictly meet the French criteria for medically assisted procreation, as defined by the 2011 Law on bioethics, were excluded ("Loi no. 2011-814 du 7 juillet 2011 relative à la bioéthique 2011-814 juillet, 2011"). Briefly, the conditions for access to ART for the general population in France are the following: couples consisting of a man and a woman sharing a common life, both living and of childbearing age (up to 43 years for women; age limit not imposed in men), with proven infertility or the need to avoid

transmission of a severe disease. For couples in which one or both partners are infected with HIV, the criteria for access to ART are defined by the French 2011 law on bioethics (2): the CD4 cell count in two samples collected 3 months apart and within 6 months before ART is higher than 200/mm^3; the couple exclusively practices protected intercourse throughout the ART process; and the plasma HIV-RNA in women who are administered HAART must be below the detection limit within 6 months before ART. In seroconcordant couples, the criteria for the eligibility of men for IVF are the same as those employed for their female partner.

At present, the majority of women infected with HIV-1 are already receiving HAART when pursuing the ART process because of the earlier indication of HAART in the general population over time or previous pregnancies that occurred after the HIV diagnosis in cases of secondary infertility (33). Of note, such early treatment during the course of HIV infection was not the standard of care throughout the study period, as the guidelines changed over time; in fact, for asymptomatic patients, this process was initially based on the CD4 cell count and comorbidities (2, 10, 33, 34).

All women were aware of their HIV infection before the onset of the ART process and had been observed over time; most of them were administered HAART. In accordance with French guidelines, their follow-up care consisted of a systematic quarterly monitoring of HIV infection (clinical status, and CD4 cell count and plasma viral load measurements) and was more frequent in the case of HIV-related symptoms, severe immunodeficiency, and/or poor compliance with or failure of antiretroviral therapy. Both partners underwent a fertility evaluation. The obstetric outcome in terms of specific maternal and fetal risks was taken into account, as is usually the case in any ART indication.

Matching Criteria and Control Group

The control group consisted of women without HIV or any other chronic viral infection such as HBV or HCV whose medical records were selected from the database of all IVF attempts in our ART center. We performed 1:1 matching according to six criteria: egg retrieval date, female age, type of infertility (primary or secondary), infertility etiology (self-insemination failures in women infected with HIV were classified as idiopathic infertility), fertilization technique (standard IVF or ICSI), and rank of the attempt (rank 1 or 2 vs. 3 or more). The case and control populations were selected after oocyte retrieval, thus excluding women rejected for IVF management because of low ovarian reserve, those whose stimulation cycles were canceled for poor response, and those whose IVF cycles were canceled due to sperm collection or oocyte retrieval failure.

Procedure

Only the first cycle of IVF or ICSI for each patient was considered during the study period. The choice of stimulation protocol, egg retrieval timing, and techniques used for the HIV-1 and control groups were based on identical criteria. The stimulation protocol was selected based on age, ovarian reserve, and previous stimulation results with the intent to achieve the best ovarian response while avoiding hyperstimulation. In the case of a normal ovarian reserve, the selected protocol was the long agonist protocol combining pituitary desensitization through the administration of a gonadotropin-releasing hormone (GnRH) agonist with stimulation using recombinant or urinary gonadotropin at doses of 150 to 300 IU for 8 to 15 days. The antagonist protocol, which combined initial stimulation with gonadotropin and the introduction of a GnRH antagonist in the late follicular phase, was usually used for patients at high risk for hyperstimulation. The flare agonist protocol was used for potential poor-responders.

Monitoring of the IVF cycle was performed every 2 to 3 days starting from stimulation day 6 using an endovaginal ultrasound and the hormone markers estradiol, luteinizing hormone (LH), and progesterone. When at least four follicles had reached 17 mm, ovulation was triggered with recombinant chorionic gonadotropin (hCG). Oocyte retrieval was performed 35 to 37 hours after the triggering of ovulation. Fertilization was performed using conventional methods or by microinjection. Embryo transfer was routinely performed on day 2 after oocyte retrieval. The transfer policy was identical for both groups and favored elective single-embryo transfer when possible (women <36 years of age and two high-quality embryos). In women with HIV-1, elective single-embryo transfer was favored to avoid multiple pregnancies, which are often associated with prematurity and worsening in the context of chronic viral infection; the cases when it was not used were based on the woman's age or embryo quality. Supernumerary embryos of good quality were frozen. Luteal phase support was achieved through the daily vaginal administration of 400 mg of progesterone.

Data Collection and Analysis

The sociodemographic data, date of HIV-1 diagnosis, the CD4 cell count and the plasma viral load within 3 months before the attempt, and the therapeutic status (whether undertaking or not undertaking HAART) of the women infected with HIV-1 were retrospectively collected in a global IVF attempt database using the IVF Procreamed software. The IVF data collected included the ovarian reserve, cycle monitoring (hormone results and ultrasound follicular count during stimulation), number of oocytes collected, embryos obtained, transferred, and frozen, and clinical pregnancies.

The main outcome was the result of the ART process: clinical pregnancy (ultrasound visualization of an embryo) and live-birth rates per oocyte retrieval and embryo transfer. The secondary end points included the fertilization rate (defined as the number of diploid zygotes/number of mature oocytes ratio), implantation rate (e.g., the ratio of implanted to transferred embryos), and obstetric and neonatal data.

The analyses were performed using Stata for Windows (version 10; StataCorp). Conditional logistic regression was used to estimate the odds ratio (ORs) and Wald 95% CI (35). The women's age, ethnicity, ovarian reserve, rank of the attempt, and fertilization method were included in the multiple regression model as potential confounders. A one-tailed *t*-test was applied to continuous data with a statistical significance threshold of $P=.05$.

The patients' medical records were retrospectively reviewed. All the data collected were anonymized in standardized forms according to the procedures detailed by the Commission Nationale de l'Informatique et des Libertés, the French information protection commission.

RESULTS

Between 2009 and 2011, 96 women infected with HIV attended our ART center, and 82 of them met the inclusion criteria for the present study: three were excluded due to HCV coinfection, two were infected with HIV-2, and three were excluded due to missing data; the IVF cycles for six couples were canceled due to sperm collection or oocyte retrieval failure. Among the 82 women infected with HIV-1, 68 were receiving HAART before undergoing ART. Although the diagnosis of HIV infection for 70% of the patients was made at least 5 years before the ART process, the exact date of HIV-1 acquisition could not be determined in most cases because some of the patients were diagnosed in a foreign country and the date of the last seronegative test was unknown. The male partners of 27% of the women infected with HIV-1 were also infected with HIV-1 compared with none in the control group.

Table 1 shows the clinical characteristics of the HIV-1 and control groups. The characteristics of both populations were statistically comparable. The average ages of the HIV-1 and control groups were 34.77 years (range: 25–43 years) and 34.85 years (range: 26–42 years), respectively (P=.89), and the distribution over four age classes was very similar. The type of infertility was secondary for 84% of the women, and the etiology was distributed mainly between tubal factor infertility (48.8%) and male factor infertility (35.4%) in both groups. The considered rank attempt was the first for two-thirds of the women. The main parameters of ovarian reserve did not differ between the HIV-1 and control groups: the antral follicle count (AFC) at 12.3 (range: 4–40) and 11.5 (range: 2–35), respectively (P=.43); and the level of antimüllerian hormone (AMH) at 3.2 ng/mL (range: 0.3–17 ng/mL) and 2.6 ng/mL (range: 0.4–11 ng/mL), respectively (P=.12). The women infected with HIV-1 more frequently originated from Sub-Saharan Africa, although a large proportion of the patients in both groups originated from Africa (82.9% vs. 61.0%, P=.002).

There were no statistically significant differences between the groups regarding ovarian stimulation, duration, total gonadotropin units received, or follicular or hormone response, although a difference in the estradiol levels was found (P=.028; Table 2). No statistically significant differences were observed in the IVF results in terms of biological indicators (number of oocytes, zygotes, and embryos), as detailed in Table 2. The HIV-1 group tended to exhibit a lower fertilization rate. No statistically significant difference in the number of embryos transferred was found between the two groups, and no statistically significant difference was found for any of

TABLE 1

Clinical characteristics of women infected with HIV-1 and controls.

Criteria	HIV-1 (n = 82)	Controls (n = 82)	*P* value
Matched			
Age (y)[a]	34.8 (25–43)	34.9 (26–42)	.89
25–29	9 (11)	9 (11)	.85
30–34	32 (39)	30 (37)	
35–39	32 (39)	31 (38)	
40–44	9 (11)	12 (15)	
Type of infertility			
Primary	13 (15.9)	13 (15.9)	1
Secondary	69 (84.1)	69 (84.1)	
Infertility etiology			
Male	29 (35.4)	29 (35.4)	1
Idiopathic	9 (11.0)	9 (11.0)	
Tubal	40 (48.8)	40 (48.8)	
Dysovulation	4 (4.9)	4 (4.9)	
Rank attempt			
1	55 (67.1)	55 (67.1)	1
2	23 (28.0)	23 (28.0)	
3	4 (4.9)	4 (4.9)	
Fertilization method			
IVF	37 (45.1)	37 (45.1)	1
ICSI/IMSI	45 (54.9)	45 (54.9)	
Non-matched			
Ovarian reserve[a]			
AMH (ng/mL)	3.16 (0.30–17)	2.61 (0.4–11)	.12
AFC (n)	12.3 (4–40)	11.5 (2–35)	.43
Ethnicity			
African	68 (83)	50 (61)	.002
Other	14 (17)	32 (39)	

Note: Values are number (percentage) unless otherwise indicated. AFC = antral follicle count; AMH = antimüllerian hormone (ng/mL); HIV-1 = human immunodeficiency virus type 1 infection; ICSI = intracytoplasmic sperm injection; IMSI = intracytoplasmic morphologically selected sperm injection; IVF = in vitro fertilization.

[a] Values are mean (range).

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TABLE 2

Ovarian stimulation and ART results in HIV-1 infected women and matched controls.

Outcome	HIV-1[a]	Controls[a]	Adjusted *P* value[b]
Ovarian stimulation			
Days of stimulation	10.6	10.6	.51
Total dose of administered gonadotropins (IU)	2,363	2,528	.24
Stimulation data at triggering			
Estradiol (pg/mL)	2,192	1,725	.028
LH (IU/mL)	2.2	2.4	.27
P (ng/mL)	0.7	0.7	.49
No. of follicles >17 mm	7.4	7	.58
Endometrium (mm for both sides)	10.5	10.3	.99
IVF results			
Oocytes retrieved	9.4	8.4	.25
Fertilized oocytes	8.0	7.3	.23
Diploid zygotes	5.0	5.0	.87
No. of embryos at day 2	4.8	4.8	.92
Fertilization rate (%)	62	68	.079
Transferable or freezable embryos	3.1	3.1	.93
High-quality embryos	0.3	0.2	.57
Transferred embryos	1.3	1.5	.11
Frozen embryos	1.8	1.7	.91

Note: AFC = antral follicle count; AMH = antimüllerian hormone (ng/mL); ART = assisted reproduction technology; HIV-1 = human immunodeficiency virus type 1; IVF = in vitro fertilization; LH = luteinizing hormone (IU/mL); P = progesterone (ng/mL).

[a] Value is the mean.

[b] Adjusted for age, ethnicity, ovarian reserve (AMH and AFC), rank attempt, and fertilization technique.

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the ovarian stimulation parameters or IVF when comparing the results of the African and the non-African women.

The assessment of issues associated with ART and pregnancy outcomes revealed that the clinical pregnancy rate in the group of women infected with HIV-1 was lower than that found in the controls (12% vs. 32%; $P=.006$). The implantation rate was also statistically significantly lower in the HIV-1 group (10% vs. 21%; $P=.022$), although the mean number of high-quality embryos at day 2 was similar (Table 3). No statistically significant differences were found between the African and non-African women.

Within HIV-1 group, there were no statistically significant differences between the women treated (n = 68) or not (n = 14) with HAART for ovarian stimulation in terms of duration, total gonadotropin units received, or follicular or hormone response, or number of oocytes, zygotes, and embryos. However, the clinical pregnancy rate was statistically significantly lower in the treated group (9% vs. 27%; $P=.068$). The same trend was observed for the implantation rate and live-birth rates, although without statistical significance (Table 4). The pregnancy and live-birth rates observed in the antiretroviral-naive women infected with HIV were close to those of the controls.

The rate of first-trimester miscarriage was high in both the HIV-1 group and the control group (45.5% and 39.3%; $P=.73$). Only one pregnancy termination (14 weeks of amenorrhea) due to age-linked trisomy 21 was observed in the HIV-1 group compared with none in the control group. The live-birth rate per transfer was statistically significantly lower in the HIV-1 group (7% vs. 19%; $P=.022$).

The characteristics of live births were the following. In the women infected with HIV-1, all five deliveries were single, term births, whereas one preterm (35 weeks of amenorrhea) twin delivery occurred in the control group. The cesarean delivery rates were similar in both groups.

The average birth weight of nonpremature newborns (>37 weeks of amenorrhea) was statistically significantly lower (2,932 g; range: 2,500–3,130 g) in the five babies born to women infected with HIV-1 compared with the weights of the 17 babies born to control mothers (3,474 g; range: 2,970–4,180 g; $P=.046$). In the HIV-1 group, none of the children had detectable plasma HIV-1 RNA levels at birth; the 2-year follow-up evaluation revealed no cases of HIV transmission. The physical examination at birth and the postnatal follow-up evaluation showed no malformations or neonatal complications in either group.

DISCUSSION

We found that the success rate of ART was reduced in terms of all studied criteria in women infected with HIV-1, although the conventional prognostic factors of ART success—such as ovarian reserve of follicles, response to hormone stimulation, and endometrial thickness—were not statistically significantly different when comparing cases and controls. Several studies have reported that the overall fertility rate is 25%– to 40% lower in women infected with HIV-1, particularly when the HIV infection is not controlled (36). These findings have been observed in developed countries where most women are evaluated and treated with antiretroviral therapy.

Inclusion and Matching Choices

In this study, women infected with HIV-1 were matched with controls according to six criteria: date of oocyte retrieval, female age, primary or secondary infertility, cause of infertility, ART technique, and the rank of attempt. Such matching enabled us to study the issues of ART in women infected with HIV-1 while avoiding most classic or known confounding factors. Only two of the previous studies on ART in women infected with HIV-1 used a matching design with controls based on the following criteria: age, cause, type and duration of infertility, and number of ART attempts (18, 25). Other previous studies were not case controlled (20–22). Matching patients based on the cause of infertility and ART techniques reduces the bias induced by the specificities of ovarian function, response to stimulation, and fertilization rate associated with male factors.

We did not take into account the HIV plasma viral load because the standard of care according to consistently followed good practice rules ensured HIV disease stability. Coinfection could not be implicated in the poor results observed in the HIV-1 group because we excluded women coinfected with HBV or HCV to avoid possible confounding factors. Indeed, previous studies have shown that HCV-infected patients exhibit a poorer response to IVF (25, 37).

TABLE 3

ART outcomes in HIV-1 infected women and matched controls.

	HIV-1 (n = 82)	Controls (n= 82)	Adjusted[a]	
Outcome	**% (n)**	**% (n)**	**OR (95% CI)**	***P* value**
Transfer/oocyte retrieval	85 (70/82)	95 (78/82)	0.23 (0.06–0.84)	.027
Clinical pregnancy/oocyte retrieval	12 (10/82)	32 (26/82)	0.30 (0.13–0.70)	.006
Clinical pregnancy/transfer	14 (10/70)	33 (26/78)	0.35 (0.15–0.83)	.017
Implantation	10 (10/104)	21 (26/122)	0.38 (0.17–0.87)	.022
Live birth/transfer	7 (5/70)	19 (15/78)	0.26 (0.08–0.82)	.022

Note: AFC = antral follicle count; AMH = antimüllerian hormone (ng/mL); CI = confidence interval; HIV-1 = human immunodeficiency virus type 1; OR = odds ratio.
[a] Adjusted for age, ethnicity, ovarian reserve (AMH and AFC), rank attempt, and fertilization technique.

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TABLE 4

Stimulation parameters and ART outcomes in HIV-1 infected women with and without HAART.

	HIV-1 ± HAART				
	+ HAART (n = 68)		− HAART (n = 14)		Adjusted[a]
Outcome	**% (n)**	**Mean**	**% (n)**	**Mean**	***P* value**
Ovarian stimulation					
Days of stimulation		10.51		10.73	.98
Total dose of administered gonadotropins (IU)		2,384		2,272	.52
Stimulation data at triggering					
Estradiol (pg/mL)		2,147		2,392	.52
LH (IU/mL)		2.23		2.19	.96
P (ng/mL)		0.67		0.70	.88
No. of follicles >17 mm		6.96		6.00	.054
Endometrium (mm for 2 sides)		10.04		12.40	.006
IVF results					
Oocytes retrieved		9.46		9.06	.78
Fertilized oocytes		8.27		6.93	.28
Diploid zygotes		5.19		4.27	.44
No. of embryos at day 2		5.16		4.07	.57
Fertilization rate (%)		0.61		0.52	.27
Transferable or freezable embryos		3.10		2.93	.62
High-quality embryos		0.33		0.33	.59
Transferred embryos		1.34		0.93	.16
Frozen embryos		1.73		2.00	.95
Outcomes					
Transfer/oocyte retrieval	88 (59/67)		73 (11/15)		.150
Clinical pregnancy/oocyte retrieval	9 (6/67)		27 (4/15)		.068
Clinical pregnancy/transfer	10 (6/59)		36 (4/11)		.015
Implantation	9 (7/90)		21 (4/14)		.128
Live births/transfer	5 (3/59)		18 (2/11)		.162

Note: AFC = antral follicle count; AMH = antimüllerian hormone (ng/mL); ART = assisted reproduction technology; HAART = highly active antiretroviral therapy; HIV-1 = human immunodeficiency virus type 1; IVF = in vitro fertilization; LH = luteinizing hormone (IU/mL); P = progesterone (ng/mL).
[a] Adjusted for age, ethnicity, ovarian reserve (AMH and AFC), rank attempt, and fertilization technique.

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Twenty-seven percent of the male partners were infected with controlled HIV-1 disease (inclusion criteria). Although some previous studies excluded HIV-seroconcordant couples (22–24), we decided to include them in our matching criteria based on the etiology of infertility and the technique (IVF or ICSI), which allowed us to perform analyses independent of the sperm characteristics. Nevertheless, it has occasionally been demonstrated that HIV-1–seroconcordant couples may present a significantly decreased pregnancy rate compared with couples in whom only the woman is infected with HIV-1 (23).

We chose to restrict the study to the population who underwent oocyte retrieval because the causes of cancellation of the ART process during ovarian stimulation were too various to be informative. They included some common medical concerns, such as inadequate response to stimulation, as well as patients withdrawing for personal reasons.

ART Parameters

As a possible explanation for our results, we did not observe any statistically significant differences in terms of the ovarian stimulation protocol, duration of stimulation, total dose of gonadotropin, peak estradiol concentration at the time of ovulation triggering, number of mature follicles expected, or thickness of the endometrium, which are predictive of embryo implantation. In the literature, the type of protocol used is seldom specified, so no comparison could be performed.

No statistically significant difference was found between the HIV-1 and control groups in terms of the number of retrieved oocytes, embryos obtained, and supernumerary cryopreserved embryos. We observed a trend toward a higher fertilization rate in the control group (P=.08). In most studies, the fertilization rate was not found to be related to the type of infertility or to the technique, regardless of whether it was higher (19, 22) or lower (25) in the group infected with HIV-1. Indeed, male indications for IVF were more frequently observed in the control group (19).

A lower number of transferred embryos was found in several studies (18, 23), and this factor was sometimes associated (24) and other times not associated (19) with a lower pregnancy rate. We did not identify a statistically significant difference between the case and control groups

that could explain the difference obtained in terms of success. The elective single-embryo transfer objectives were met when possible, and the goal was achieved in our population because we did not observe any twin pregnancies in the HIV-1 group.

Pregnancy and Birth Rates

In our study, although the number of high-grade embryos did not differ between the two groups, the implantation rate was statistically significantly lower in the HIV-1 group. Our low implantation rate of approximately 11% is in agreement with that previously reported in most studies, with the exception of one study that reported no statistically significant difference (23).

The clinical pregnancy rates per oocyte retrieval and per transfer were also statistically significantly lower in the group with HIV-1 infection compared with the controls (OR 0.30, 0.13–0.70 and OR 0.35, 0.15–0.83, respectively). Similar results were reported by Coll et al. (24), who compared the pregnancy rates of women infected with HIV-1 with those of age-matched controls. No difference was found in women infected with HIV-1 who benefited from egg donation, highlighting the hypotheses that the oocyte quality was altered due to exposure to the virus and/or that HAART was partially responsible for the decreased pregnancy rate. Santulli et al. (23) compared the results between women infected with HIV-1 and negative controls matched by age and HIV-1 serologic status of the male partner; they found a lower pregnancy rate in the HIV-1 group, but this finding was only obtained when the male partner was also infected with HIV-1. The duration of infertility was longer in women infected with HIV-1, which could partially explain the results. The live-birth rate per embryo transfer was also lower in the HIV-1 group than in the control group ($P=.022$). These data are rarely detailed in the literature because data collection is usually limited to results in terms of early pregnancy. The limited number of term pregnancies did not allow us to draw conclusions regarding malformations or rare diseases.

Impact of Ethnicity on Poorer Outcomes of ART in Women Infected with HIV-1

The role of ethnic disparities has mainly been studied in the United States, as detailed in the literature. Poorer ART outcomes have been reported in African American populations, but the role of ethnicity, environmental, or economic factors is still debated (38–40). In France, given ethical considerations, only the geographic place of birth of our patients is available in our medical database.

In our study, women originally from Africa were more represented in the HIV-1 group, but some (albeit a smaller number) were also included in the control group. For this reason and because ethnicity matching was not possible, the geographic origin was included in the multiple regression model as a potential confounder, as indicated in the data collection and analysis section, and no effect was found.

Impact of the Duration of HIV Infection and Antiretroviral Treatment on ART Outcomes

The question of the impact of the duration of HIV infection on the results of IVF should be considered (23). In 70% of our study population, the HIV infection was diagnosed at least 5 years before ART, but the exact date of HIV-1 acquisition could not be determined for any of the women. Thus, the relationship between the duration of the disease and the IVF success rate could not be reliably analyzed.

When considering the study population and period, 14 of the 82 women infected with HIV-1 were HAART-naïve at start of the IVF process, which is not enough to allow a firm conclusion regarding the comparison between the HAART-treated and HAART-untreated groups. Nevertheless, we observed that HAART-treated women had a statistically significantly poorer response to fertility treatment than the HAART-naïve women. The pregnancy and live-birth rates in antiretroviral naïve women were close to those of the controls. We cannot exclude that women receiving HAART may have poorer responses to fertility therapy because of more advanced HIV disease as compared with HAART-naïve women. The fertility treatment response could also be linked to HAART toxicity (32), particularly on ovaries and oocyte quality. Indeed, mitochondrial toxicity is a well-known side effect of nucleoside reverse transcriptase inhibitors (2, 29). Statistically significantly lower mitochondrial DNA content has been previously reported in women with lower ovarian reserve (116 oocytes, 47 women) (41, 42). Lopez et al. (30) reported a statistically significant decrease in mitochondrial DNA in the oocytes of women receiving HAART treatment for more than 9 years compared with the oocytes of women who were not infected with HIV.

Future Prospects

The current French bioethics laws enacted in July 2011 stipulate that any person whose medical care is likely to impair fertility or whose fertility may be impaired prematurely can benefit from the collection and preservation of gametes or germinal tissue for the subsequent realization of ART. Our data argue that women infected with HIV-1 with controlled diseases whose fertility may be impaired prematurely should be eligible for such procedures, including vitrification (i.e., ultrarapid freezing of oocytes).

CONCLUSION

In this match-paired case-control study, the rates of implantation, clinical pregnancy, and live birth were all statistically significantly lower in women infected with HIV-1 than in the uninfected control group. The considerations stemming from this study and those presented in the literature validate the need to inform physicians caring for women infected with HIV about the poorer performance of ART in women who are infected with HIV-1 compared with the general population. Accordingly, preconception care, as recommended by the current French guidelines, should permit advising these women, if their health allows, to limit their self-insemination attempts to a year without success and not to

postpone a fertility assessment. These recommendations are essential for women aged 35 years and older whose ovarian reserve is physiologically compromised. Future prospects include considering the indications of fertility preservation by the vitrification of oocytes of women whose pregnancy should be delayed.

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