Journal of Virus Eradication 2019; **5**: 44–46

Case series of infertility amongst young women with perinatally acquired HIV: data from a London cohort

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Abstract

Introduction: Increased rates of infertility have been reported in women who acquired HIV horizontally compared to population age-matched normative data. However, few data exist for adults with perinatally acquired HIV (PaHIV), who have been exposed to antiretroviral drugs and/or HIV-associated ill health through childhood and puberty. We describe a case series of infertility amongst women with PaHIV attending a London clinic between 2006 and 2017.

Methods: A retrospective case-note review was conducted amongst all female PaHIV patients aged >16 years attending a London clinic. All data was captured into an electronic database using paper and electronic clinical records taken from every routine clinic visit (average three times/year between 2006 and 2017). Data captured included HIV viral load, CD4 cell count, antiretroviral therapy regimen, sexual and reproductive health and STI screening. Age-matched analysis of infertility rates compared to the general population were not performed.

Results: In total, 119 young women were included, with a median age of 20 years (interquartile range [IQR] 18–24, range 16–33 years) at latest follow-up. Three women with PaHIV were diagnosed with infertility (*n*=3): two with primary ovarian insufficiency (*n*=2) and one with hypogonadotropic hypogonadism (*n*=1). A further 5/116 (4.3%) were under investigation for menstrual irregularities. Of the remaining 111 young women, 17 (15%) had successfully conceived. All patients were currently prescribed ART, with 93 (78%) having an HIV VL <50 copies/mL at their last visit. Median ART exposure was 13 (IQR 9–17) years. Among five women with reported irregular menstrual cycles there was no correlation with current CD4 cell count, HIV VL or length of ART exposure, although there was an increased prevalence of body mass index >25 kg/m^2 (63% *vs* 30%).

Conclusion: Overall the reproductive health status for young women with PaHIV was comparable to the general population.

Keywords: HIV, perinatal HIV infection, women, infertility

Introduction

Improved access and safety of effective antiretroviral therapy (ART) globally has led to significant improvements in survival for all people living with HIV [1]. More children with perinatally acquired HIV (PaHIV) are surviving into adulthood.

An increased prevalence of infertility has been observed in women living with horizontally acquired HIV (HaHIV) compared to an age-matched population without HIV [2]. In addition, studies amongst women with horizontally acquired HIV reported higher incidences of idiopathic tubal occlusions and tubo-ovarian abscess formation [3], prolonged periods of amenorrhoea and early onset of menopause compared with women without HIV [4]. Several proposed explanations might account for these observations: impaired immune response to gynaecological infections such as chlamydia [5]; adverse endocrinological effects of HIV on ovarian function [4]; and ART mitochondrial toxicities vital in ovum development [6]. Anti-Müllerian hormone (AMH), used as a biomarker of ovarian reserve, has shown to be lower in women with horizontally acquired HIV compared to controls without HIV [7].

Although fertility has been investigated in adults with horizontally acquired HIV, there are few data on adults living with PaHIV from birth. We describe reported reproductive health status and three cases of infertility amongst young women with PaHIV attending a London clinic.

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Methods

We undertook a cross-sectional observational study including all female patients aged >16 years with PaHIV attending adolescent and young adult services at a London centre between 2006 and July 2017. All female patients are reviewed and monitored two to four times per year in accordance with British HIV Association (BHIVA) guidelines, including discussions about sexual and reproductive health [8]. Appropriate specialist referral was made on the basis of reproductive health concerns such as difficulty conceiving or menstrual abnormalities. Retrospective case-note review and analysis using electronic clinical patient data were performed. Person identifiers were not used in the analysis and young women who acquired HIV horizontally and were attending the service were excluded. Median and interquartile ranges (IQR) were used to summarise numerical variables, with percentages used to summarise categorical variables. This study was undertaken as an audit and hence research ethical approval was not sought. All missing data were presumed to be missing at random.

Results

General description of cohort

The cohort consisted of 119 women with PaHIV with patient demographics shown in Table 1. The median age was 20 (IQR 18–24) years with 100 (84%) were of black or mixed ethnicity. All women were currently being prescribed ART with 93 (78%) having an HIV VL <50 copies/mL at their last visit. Of the 17 women who had successfully conceived, the median age at first pregnancy was 21 (IQR 18–25) years.

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Table 1. Demographic and clinic characteristics of the cohort of women with PaHIV (total=119)

	Pregnant* (total=17)	Whole cohort (total=119)
Median age (years) (IQR)	25 (23–28)	20 (18–24)
Mean BMI (kg/m^2)	21.74	24.18
Underweight (BMI <18.5 kg/m^2) (*n*)	1 (6%)	4/93 (4%)
Overweight (BMI >25 kg/m^2) (*n*)	1 (6%)	30/93 (32%)
Black or mixed ethnicity (*n*)	15 (88%)	100/119 (84%)
Median CD4 cell count at time of audit (cells/mm^3) (IQR)	539 (285–737)	666 (479–853)
Median CD4 cell count at time of pregnancy (cells/mm^3) (IQR)	439 (213–690)	–
Median nadir CD4 (cells/mm^3) (IQR)	256 (70–390)	320 (148–479)
Undetectable VL <50 copies/mL at time of audit (*n*)	10 (59%)	93 (78%)
Individuals using alcohol (*n*)	8/14 (57%)	49/109 (45%)
Individuals smoking (*n*)	10 (59%)	26/113 (23%)
Median years ART exposure (IQR)	12 (9–15)	13 (9–17)
Exposed ever to AZT, ddI or d4T (*n*)	8 (47%)	50/95 (53%)
Previous AIDS-defining diagnosis (*n*)	6 (35%)	42/110 (38%)

AZT: zidovudine; BMI: body mass index; ddI: didanosine; d4T: stavudine; PaHIV: perinatally acquired HIV; VL: viral load.
*There were 26 pregnancies and 20 live births. All infants had tested HIV negative to date. Three women had been seen by fertility services prior to conception.

Self-reported menstrual irregularities

Eight out of 119 (6.7%) women self-reported menstrual irregularities and were referred to specialist services, three of whom received an infertility diagnosis. Five out of those eight (63%) were overweight (body mass index [BMI] >25 kg/m^2) and 25/84 (30%) of the remaining cohort were overweight. Of the five women under investigation by gynaecology, four were diagnosed with polycystic ovarian syndrome (PCOS) and one had uterine subserosal fibroids. Patients with PCOS were offered follow-up hormone level testing and were recommended to adjust weight to a BMI where menstrual cycles would be regular.

Confirmed infertility cases

Case 1

A 22-year-old British African woman with PaHIV was referred to the gynaecologist and was diagnosed with primary ovarian insufficiency (POI) based on reports of secondary amenorrhoea since age 19 years. Her menarche was at the age of 14 and she had regular periods. She had been adherent to her ART regimen (abacavir, dolutegravir, lamivudine) with suppressed VL for 9 consecutive years. She had a background of borderline hypercholesterolaemia and a nadir CD4 cell count of 360 cells/mm^3. Physical examination was unremarkable with a BMI of 30.3 kg/m^2. Laboratory findings revealed high serum FSH (33 and 40.8 IU/mL); low serum oestradiol (70 pmol/L); CD4 cell count of 565 cells/mm^3, and an undetectable VL. Pelvic ultrasound demonstrated a small anteverted uterus with no focal lesions with a very thin 2.5mm endometrium. The management plan was long-term hormone replacement therapy (HRT) and protection of bone health with a normal karyotype and negative fragile X screening.

Case 2

A 26-year-old British African woman with PaHIV was referred to endocrinology at the age of 16 years with no pubertal development and primary amenorrhoea. She had a nadir CD4 cell count of 570 cells/mm^3 and her latest CD4 cell count was 1127 cells/mm^3 with an undetectable VL. She had 2 consecutive years of suppressed virus with her current ART regimen (abacavir, dolutegravir, lamivudine). She commenced on ethinylestradiol with an increasing dose to induce puberty. She remained amenorrhoeic despite undergoing partial pubarche and thelarche. At aged 18, failure to identify ovaries via transvaginal ultrasound, prompted laparoscopy revealing streak ovaries and a normal uterus. At aged 21 years, the patient underwent further endocrinological investigations. The karyotype was 46XX. Basal hormonal evaluation revealed low serum oestradiol (<37.0 pmol/L), high serum prolactin (205 ng/mL), suppressed LH (0.1 IU/L) and FSH (0.8 IU/L) levels. Anterior pituitary function was normal, including normal thyroid function (TSH 1.18 mIU/L; free T4 14.7 pmol/L) and a normal short synacthen test. Magnetic resonance imaging of the hypothalamic-pituitary region was normal. However, an acute GnRH stimulation test demonstrated reduced pituitary reserve and a re-diagnosis of hypogonadotropic hypogonadism was made.

She was managed with transdermal oestradiol with norethisterone. Her medication was changed to an oral preparation due to development of a non-pruritic rash on her forehead and lower legs. At aged 24 years, she had a levonorgestrel-containing intrauterine device for 2 years and the oestrogen preparation was switched to pure oestradiol valerate. She remained adherent to her ART regimen, with a latest CD4 cell count of 1127 cells/mm^3 and an undetectable VL. With the intention to conceive with her regular partner in the future, a gynaecological referral was made and she was offered to a trial of ovarian stimulation with human menopausal gonadotropin.

Case 3

A 28-year-old woman, adopted from Romania was diagnosed with HIV and hepatitis B (with test results as follows: HBsAg negative; PCR negative; HBeAb and HBcAb positive) at the age of 7 months. She commenced ART in 1997 but with poor adherence in childhood developed triple class resistance, a nadir CD4 cell count 160 cells/mm^3, with failure to thrive and delayed puberty. Childhood ART exposure included zidovudine, didanosine, stavudine, lamivudine, abacavir, tenofovir, nelfinavir, lopinavir/ritonavir and efavirenz. At 16.5 years chronological age, her bone age was 12 years and with persistent primary amenorrhoea referral to gynaecology was prompted at age 18 years and POI was diagnosed. She remained amennorrhoeic, declined

hormone replacement therapy and vitamin D supplementation and subsequently transferred care in 2010 with a CD4 cell count of 160 cells/mm^3 and VL 63,863 cells/mL. She also developed lipodystrophy, depression and noncirrhotic portal hypertension presumed secondary to didanosine [9].

Discussion

This is one of the first reports on reproductive health outcomes for young women with PaHIV. From this small cohort we identified three individuals (2.5%) with confirmed infertility. The majority of women who experienced menstrual abnormalities were diagnosed with PCOS. Previous literature highlighted a number of adolescents with PaHIV diagnosed with PCOS, yet the exact mechanism between metabolic complications of chronic ART and susceptibility to developing PCOS is unknown [10–12]. Several mechanisms may contribute to impaired reproductive health amongst this particular group including chronic ill health, exposure to ART-related toxicities, failure to thrive in childhood, and ongoing HIV-associated inflammation and immune system modulation through puberty. Overall, the reproductive health status for young women with PaHIV was comparable to the general population [13].

We report two cases of women with PaHIV diagnosed with POI and one case of hypogonadotropic hypogonadism. Interestingly, a prospective pilot study by Ohl *et al*. showed 85% of HIV-infected women have at least one out of four abnormal parameters of ovarian reserve whilst the disparity in ovarian function increases with age [14]. The aetiology of follicle depletion or dysfunction is diverse [15]. Early diagnosis of POI and multidisciplinary careful long-term management are essential to prevent associated comorbidities such as osteoporosis and optimise quality of life.

A major limitation of this study is the retrospective observational design and small study number. Therefore, the generalisability of these findings is uncertain; however, as more young women with PaHIV survive into adulthood additional data will inform future fertility. Furthermore, most individuals in the current cohort have yet to try to conceive, reflecting their young age and known history of contraception, so these data are preliminary findings. At each clinic visit, as appropriate, discussion around sexual and reproductive health is offered, which is an important part of providing holistic care for people living with HIV. We demonstrate timely management of rare cases of infertility for young women with PaHIV, and anticipate informative additional data over time.

Acknowledgements

Conflicts of interest and source of funding

None

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