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Pregnancies in older women living with HIV in the United Kingdom and Ireland

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Abstract

Objectives: To compare maternal characteristics and pregnancy outcomes in women aged <40 years and ≥40 years in a large unselected population of HIV-positive women delivering in the UK and Ireland between 2000 and 2014.

Methods: Comprehensive population-based surveillance data on all HIV-positive pregnant women and their children seen for care in the UK and Ireland are collected through the National Study of HIV in Pregnancy and Childhood. All singleton and multiple pregnancies reported by the end of June 2015 resulting in live birth or stillbirth to women diagnosed before delivery and delivering in 2000-2014 were included. Logistic regression models were fitted in analyses examining the association between older maternal age and specific outcomes (preterm delivery and stillbirth).

Results: Among 15,501 pregnancies in HIV-positive women, the proportion in older women (≥40 years) increased from 2.1% (73/3419) in 2000-2004 to 8.9% (510/5748) in 2010-2014 (p<0.001). Compared with pregnancies in younger women, those in older women were more likely to result in multiple birth (3.0% versus 1.9%, p=0.03), stillbirth (adjusted odds ratio 2.39, p=0.004) or an infant with a chromosomal abnormality (1.6% versus 0.2%, p<0.001). However, there was no increased risk of preterm delivery, low birth weight or mother-to-child HIV transmission among older mothers.

Conclusions: There has been a significant increase over time in the proportion of deliveries to women living with HIV aged 40 years or more, which has implications for pregnancy management, given their increased risk of multiple births, stillbirth and chromosomal anomalies, as also apparent in the general population.

Keywords: HIV; pregnancy outcomes; maternal age; stillbirth; surveillance

Introduction

Pregnancy incidence among women living with HIV has increased in recent years (1, 2) alongside increases in life expectancy (3) and a decline in mother-to-child HIV transmission (MTCT) rates to less than 1% in some regions (4, 5). In many countries in North America and Europe, including the United Kingdom (UK), maternal age has been increasing both in the general obstetric population (6) and among HIV-positive women (7). Advanced maternal age in pregnancy (over 35 or 40 years) is associated with an increased risk of obstetric complications including pre-eclampsia, gestational diabetes, preterm birth and stillbirth (8, 9). In addition, both HIV infection and antiretroviral therapy in pregnancy are themselves risk factors for adverse pregnancy outcomes such as preterm birth (10). There is to date little research on the small but increasing group of women with both HIV- and age-related risks during pregnancy (11, 12). One small study in the United States found a significantly higher rate of preterm delivery among HIV-positive (41%) compared with HIV-negative (17%) women aged over 35 years (12). High rates of illicit drug use were also reported in the study population (28% and 14% respectively), although the association between HIV infection status and preterm delivery remained after adjusting for this. A larger study in Italy (11) found higher rates of preterm delivery and low birth weight in HIV-positive mothers ≥35 years of age compared with mothers <35 years, but the association was not significant in multivariable analysis. The authors reported no differences by maternal age in rates of congenital abnormalities or other pregnancy complications (e.g. hypertension, diabetes or anaemia) or delivery complications (11).

Our objective was to compare maternal characteristics and pregnancy outcomes in women aged <40 years and ≥40 years in a large unselected population of HIV-positive women delivering in the UK and Ireland between 2000 and 2014.

Methods

Comprehensive population-based surveillance data on all HIV-positive pregnant women and their children seen for care in the UK and Ireland are collected through the National Study of HIV in Pregnancy and Childhood (NSHPC) (4, 7). Information on pregnancy and delivery are collected from obstetric respondents in each maternity unit, and HIV-exposed infants are followed up through their paediatricians to establish infection status. Full methodological details are described elsewhere (4, 7). All singleton and multiple pregnancies reported by the end of June 2015 resulting in live birth or stillbirth to HIV-positive women diagnosed before delivery and delivering between 2000 and 2014 were included.

UK guidelines recommend that pregnant women should book for antenatal care by around 10-13 weeks gestation and that all women should routinely be offered ultrasound screening for fetal anomalies at 18-20 weeks gestation. Screening policies for Down's Syndrome have varied over time; in 2003 it was recommended that all women should be offered screening, and since 2008, that this should be performed by the end of the first trimester.

Maternal age was categorised as <40 ("younger women") or ≥40 years ("older women") at the time of delivery, as numbers were sufficiently large (over 850 women ≥40 years) to focus on this higher risk group. Year of delivery was grouped into five-year periods: 2000-2004, 2005-2009, and 2010-2014. Mode of delivery was classified as elective caesarean section (pre-labour, pre-rupture of membranes), emergency caesarean section (after rupture of membranes and/or onset of labour, or for other emergency obstetric indications), or vaginal delivery. Information on operative vaginal delivery was only collected from July 2008 onwards. Delivery at <37 completed weeks was classified as preterm. Maternal HIV viral load was measured closest to delivery (30 days before or up to seven days postpartum) and categorised as <50 (undetectable), 50-399, 400-999, 1000-9999, and ≥10,000 copies/ml. Maternal CD4 cell count closest to delivery was classified as <200, 200-349, 350-499 and ≥500 cells/mm^3. Congenital abnormalities were classified according to the World Health

Organization International Classification of Diseases version 10 (13). Infant HIV infection status was established based on PCR tests carried out after one month of age (4)

Data were managed in Access 2010 (Microsoft Corp., Redmond, Washington, USA) and analysed using Stata version 12.1 (Stata Corp. LP, College Station, Texas, USA). Means were compared using *t*-tests and medians using Wilcoxon tests. Trends in medians were assessed using Cuzick's nonparametric test for trend across ordered groups (function 'nptrend' in Stata). Logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs) in analyses examining the association between older maternal age and a) preterm delivery and b) stillbirth. In multivariable analyses, variables were included in the model if they were considered potential confounders and significantly improved the model's goodness of fit (significance level $p<0.10$). To allow for repeat pregnancies in the same woman in preterm delivery analyses only (as <5 women experienced more than one stillbirth), generalized linear mixed effects were used to fit logistic regression models accounting for random effects attributed to the mother (14).

The National Study of HIV in Pregnancy and Childhood has London Multi-Centre Research Ethics Committee approval (MREC/04/2/009).

Results

Overall 15,501 pregnancies in 10,997 women delivering in 2000-2014 were included, 856 (5.5%) of which were in women aged ≥40 years at delivery. Most pregnancies (79%) were in women from sub-Saharan Africa, and only 2% in women who acquired HIV through injecting drug use (Table 1). First antenatal appointment (collected since 2008) occurred at a median of 12.4 weeks gestation (interquartile range (IQR) 10.1, 16.0, n=7154 pregnancies). Median maternal age was 31.5 years (IQR 27.6, 35.4, range 14.5, 50.6), increasing over time from 29.6 years in 2000-2004, to 31.0 years in 2005-2009, and 33.2 years in 2010-2014 (trend $p<0.001$). The proportion of pregnancies in older women (≥40 years at delivery) also increased significantly over time, from 2.1% (73/3419) in 2000-2004, to 4.3% (273/6334) in 2005-2009, and 8.9% (510/5748) in 2010-2014 (trend $p<0.001$).

Similar patterns were observed among pregnancies in primiparous women (*n*=4408), with an increase in those ≥40 years from 0.9% (10/1112) in 2000-2004, to 2.0% (39/1923) in 2005-2009, and 5.2% (71/1373) in 2010-2014 (trend *p*<0.001) (2.7% overall, 2000-2014). Median maternal age among pregnancies in primiparous women was 28.8 years, increasing from 27.2 years in 2000-2004 to 28.5 years in 2005-2009 and 30.6 years in 2010-2014 (trend *p*<0.001).

Compared with pregnancies in younger women, those in older women were more likely to be in women with three or more previous births, and in those diagnosed with HIV before their pregnancy (Table 1). There were no differences by age group in maternal region of birth, HIV risk factor (injecting drug use or other/unknown), or type of combination antiretroviral therapy (cART) in pregnancy (Table 1).

However, treatment in pregnancy, and at conception, was more likely for pregnancies in older women, and cART was started slightly earlier compared with pregnancies in younger women (median week of cART initiation 22.8 versus 23.5 weeks, p=0.02), even though there were no differences in timing of first antenatal appointment (median 14 weeks for both groups, *p*=0.88). Pregnancies in older women were more commonly associated with suppressed viral load at delivery than those in younger women, and with low CD4 count (<200 cells/µl) (Table 1), although median CD4 cell count did not differ by maternal age group: 431 cells/µl among younger women versus 445 cells/µl among older women (*p*=0.19). The viral load difference was restricted to women starting treatment in pregnancy (viral load was suppressed in 74.9% (143/191) of pregnancies in older versus 63.3% (3506/5536) of those in younger women), and was not apparent where women were on treatment at conception (p=0.71).

There was no evidence of an increased rate of emergency caesarean section or operative vaginal delivery among pregnancies in older compared with younger women, but the risk of multiple births and an infant with a chromosomal abnormality was higher (Table 2). There was no increased risk of preterm delivery (<37, <34 or <32 weeks) or low birth weight among deliveries to older compared with younger women (Table 2); there was a suggestion that infants of older women were more likely

to have very low (<1.5 kg) or high (≥4 kg) birth weight but neither association reached statistical significance. In multivariable analysis of singleton pregnancies adjusting for time period, injecting drug use (reported as the route of maternal HIV acquisition) and type of antiretroviral therapy (cART versus 1-2 antiretroviral drugs, excluding untreated pregnancies), maternal age ≥40 years was not significantly associated with preterm delivery (<37 weeks) (adjusted OR (AOR) 1.21, 95% CI 0.92, 1.60, *p*=0.18). All other variables included in the model were significantly associated with the outcome (p<0.05).

More pregnancies in older mothers ended in stillbirth (1.6% versus 1.0%), although this did not reach statistical significance in univariable analysis (OR 1.70, 95% CI: 0.99-3.01, p=0.05). After adjusting for time period, parity (0, 1+ previous births) and type of antiretroviral therapy (as above), the strength of this association increased and was statistically significant (AOR 2.39, 95% CI 1.32, 4.32, *p*=0.004); in this model, the only other variable significantly associated with the outcome was time period. There was no difference in the MTCT rate according to maternal age (Table 2). Thirteen maternal deaths were reported, but none were in older mothers.

Discussion

In this population-based surveillance study of HIV-positive pregnant women, we observed a significant increase over time in median maternal age, and in the proportion of deliveries to women aged over 40 years, such that in the most recent time period, 9% of all deliveries were to women aged ≥40 years. Compared with pregnancies in younger HIV-positive women (<40 years), those in older women were significantly more likely to result in multiple births and an infant with a chromosomal abnormality. Pregnancies in older women were also more likely to result in stillbirth (1.6% versus 1.0%); although not statistically significant in univariable analysis, it was significant after adjusting for time period, parity and cART. There was no evidence that older maternal age was associated with an increased risk of preterm delivery, low birth weight or MTCT in this population.

Our findings are consistent with studies in the general population showing an association between advanced maternal age and outcomes such as multiple pregnancy (15), chromosomal abnormalities (16), and stillbirth (8, 17). Data on multiple maternity rates in England and Wales for 2014 are consistent with our results, with a rate of 2.9% for women aged 40-44 years (compared with 3.0% here) and ranging from 0.96% for 20-24 year olds to 2.3% for 35-39 year olds (compared with 1.9% here for <40 year olds) (18). Higher twinning rates in older women may reflect a biological propensity for multiple births as well as higher rates of fertility treatment; we were unable to explore the contribution of fertility treatment to the multiple birth rate here as we do not collect this information.

The doubling of risk of stillbirth associated with maternal age over 40 years is of a similar magnitude to that estimated through meta-analysis of five studies in the general obstetric population in high income countries (8). The stillbirth rates in HIV-positive women were higher than in the general population (0.47% overall, 0.76% for 40-44 year olds and 0.95% for ≥45 year olds), with the greatest difference seen for younger women (18). However, unlike other studies (17, 19) we did not observe an increased risk of preterm delivery, although the rate was higher overall than in the general population (13.2% versus 6.2%) (20). It was also reassuring that rates of emergency caesarean section and operative vaginal deliveries were not significantly increased in older mothers in this study.

Overall, most pregnancies were in women already aware of their HIV status from before conception, and the greater proportion of older women in this group likely reflects greater opportunity for HIV testing, particularly in previous pregnancies, given their higher parity. As a result, a higher proportion of pregnancies in older women were conceived on cART, whilst those in which cART was started in pregnancy were more likely to have an undetectable viral load at delivery; this latter finding is consistent with other studies and may reflect better adherence in older people (21) as well as more effective and less toxic antiretroviral drugs in later calendar years, when most pregnancies in older women occurred.

The NSHPC is a well-established, ongoing surveillance study which aims to include all pregnancies in HIV-positive women in the UK and Ireland and has high response rates. However, limited data are collected on background characteristics and clinical measures in pregnancy, and we had no information on factors such as smoking, or history of complications such as hypertension or delivery complications. Our findings are likely generalizable to other Western European HIV pregnancy cohorts which have similarly high proportions of sub-Saharan African migrants (22,23).

This report highlights an increase over time in pregnancies among HIV-positive women aged 40 years or more. These findings have implications for pregnancy management of older HIV-positive women, given the increased risk of multiple births in this group, as well as pre-existing co-morbidities and adverse outcomes such as stillbirth and chromosomal anomalies, as has been reported in the HIV-negative population.

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Contribution to authorship

CLT carried out the statistical analyses. CLT, AdR and CT drafted the paper, and all authors contributed to interpreting the results, and critically revising the article. CT is responsible for the NSHPC and is the guarantor.

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Table 1. Baseline maternal characteristics for pregnancies in HIV-positive pregnant women according to age at delivery (<40 years or ≥40 years at delivery)

	Maternal age at delivery				
	<40 years		≥40 years		*p*-value
	n	%	*n*	%	(X^2)*
Maternal region of birth (*n*=15375)					
UK/Ireland	2061	14.2	100	11.8	
Africa	11093	76.4	670	79.2	
Elsewhere	1375	9.5	76	9.0	0.1
HIV risk factor (*n*=15501)					
Other risk	14343	97.9	839	98.0	
IDU	302	2.1	17	2.0	0.9
Timing of diagnosis (*n*=15477)					
Before this pregnancy	9385	64.2	715	83.6	
During this pregnancy	5237	35.8	140	16.4	<0.001
Parity (number of previous births) (*n*=14497)					
None	4288	31.3	120	14.8	
One	4953	36.2	213	26.3	
Two	2870	21.0	210	25.9	
Three or more	1575	11.5	268	33.0	<0.001
Type of ART (*n*=15329)					
Untreated	248	1.7	6	0.7	0.03*
ZDV monotherapy	860	5.9	19	2.2	
Dual therapy	134	0.9	7	0.8	
cART (3 or more drugs)	13239	91.4	816	96.2	<0.001

cART drug class (*n*=14055)					
NRTI + NNRTI	4234	32.0	286	35.1	
NRTI + PI	8075	61.0	474	58.1	
NRTI + PI + NNRTI	665	5.0	36	4.4	
Other combinations*	265	2.0	20	2.5	0.2
cART at conception (*n*=13882)					
No	7984	61.1	268	33.2	
Yes	5091	38.9	539	66.8	<0.001
HIV RNA viral load closest to delivery (copies/ml) (*n*=9181)**					
<50	6226	72.0	457	85.4	
50-999	1758	20.3	53	9.9	
1000-9999	415	4.8	13	2.4	
≥10,000	247	2.9	12	2.2	<0.001
CD4 cell count (cells/µl) (*n*=14036)					
≥500	5042	38.1	318	39.6	
350-499	3780	28.6	242	30.1	
200-349	3143	23.8	192	23.9	
<200	1268	9.6	51	6.4	0.02

ART, antiretroviral therapy; cART, combination antiretroviral therapy; IDU, injecting drug use; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; UK, United Kingdom; ZDV, zidovudine. * Includes triple NRTIs and regimens containing integrase inhibitors. ** From 30 days before to 7 days after delivery.

Table 2. Pregnancy outcomes according to maternal age at delivery (<40 years or ≥40 years at delivery)

	Maternal age at delivery				
	<40 years		≥40 years		*p*-value
	%	(n/N)	%	(n/N)	(X^2)
Emergency caesarean section (*n*=14567)	23.9	(3487/14567)	25.7	(218/849)	0.2
Operative vaginal delivery (*n*=6203*)	4.6	(265/5712)	3.1	(15/491)	0.1
Stillbirth (*n*=15501)	1.0	(146/14645)	1.6	(14/856)	0.07
Multiple birth (*n*=15501)	1.9	(285/14645)	3.0	(26/856)	0.03
Preterm delivery (*n*=15464)					
<37 weeks	13.1	(1919/14609)	14.3	(122/855)	0.3
<34 weeks	5.2	(753/14609)	6.1	(52/855)	0.2
<32 weeks	3.2	(469/14609)	4.2	(36/855)	0.1
Low birth weight (*n*=14399)					
<2.5 kg	14.1	(1910/13585)	14.4	(117/814)	0.8
<1.5 kg	2.8	(376/13585)	3.8	(31/814)	0.08
Birth weight ≥4 kg (*n*=14399)	3.4	(469/14399)	4.7	(38/814)	0.07
Congenital Abnormality (*n*=15041)	2.8	(403/14212)	4.2	(35/829)	0.02
- Chromosomal	0.2	(31/14212)	1.6	(13/829)	<0.001
- Structural	2.6	(372/14212)	2.7	(22/829)	0.9
MTCT (*n*=13031)	0.8	(105/12381)	0.6	(4/650)	0.5

MTCT, mother-to-child HIV transmission. * Information on operative vaginal delivery was only collected from July 2008 onward.