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Risk factors during pregnancy – and birth-related complications in HIV-positive versus HIV-negative women in Denmark 2002-2014

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Abstract:

Objectives:

We aimed to compare risk factors for adverse pregnancy outcomes in women living with HIV (WLWH) with women of the general population (WGP) in Denmark. Further, we estimated risk of pregnancy- or birth-related complications.

Methods:

A retrospective cohort study including all WLWH who delivered a live-born child from 2002-2014 and controls, matched by origin, age, year and parity. We compared risk factors during pregnancy and estimated risk of pregnancy- and birth-related complications using multivariate logistic regression.

Results:

A total of 2,334 pregnancies in 304 WLWH and 1,945 WGP were included. WLWH had more risk factors present during pregnancy: previous caesarean section (CS) (24.7% vs 16.3%; *p*=0.0001), smoking (14.2% vs 7.5%; *p*=0.0001) and previous perinatal/neonatal death (2.3% vs 0.9%; *p*=0.03).

We found no difference between groups regarding gestational diabetes, hypertensive disorders, low birth weights or premature delivery. More children of WLWH had intrauterine-growth-retardation (IUGR) (aOR 1.9 95%CI; 1.1-3.2; *p*=0.02). Median gestational age and birth weights were lower in children born to WLWH.

WLWH had higher risk of emergency CS (EmCS) (aOR 1.6 95%CI; 1.2-2.1; *p*=0.0005) and postpartum haemorrhage (aOR 1.4 95%CI; 1.0-1.9; *p*=0.02) but not infection, amniotomy, failure to progress, low APGAR scores or signs of asphyxia.

Conclusion:

WLWH had more risk factors present during pregnancy, similar risk of most pregnancy- and birth-related complications but a higher risk of postpartum haemorrhage and EmCS than WGP. Children born by WLWH had lower median birth weights and gestational age and were at higher risk of IUGR.

Introduction

Management of pregnant woman with HIV infection has evolved significantly over the past 25 years in light of advancements in antiretroviral therapy (ART) and a better understanding of the prevention of perinatal HIV transmission. In the United States and Europe the risk of mother-to-child transmission (MTCT) in women living with HIV (WLWH) with viral suppression and who do not breastfeed is <1% independently of mode of delivery (1-3).

Pregnancy in WLWH compared with women of the general population (WGP) has been associated with several adverse outcomes to both mothers and infants (4, 5). Possible maternal complications include preeclampsia, gestational diabetes and premature rupture of membranes (PROM). Moreover the birth itself brings the mother at risk of several other harmful events including emergency caesarean section (EmCS), post-partum-bleeding and infections (6-10). Previous studies have shown that children born by WLWH are at higher risk of prematurity, asphyxia, growth-restriction and low birth weight (6, 11, 12). However much of the research have shown contradictory results (5, 6, 11, 13-15), which may be explained by differences in national recommendations and changing guidelines regarding ART and mode of delivery. It has been questioned if pregnant WLWH constitutes a subpopulation with risk factors beyond HIV causing bias to results (9)

Vaginal delivery is a safe mode of delivery in WLWH with viral suppression and does not increase risk of MTCT (3, 10, 16). However, far more WLWH still deliver by caesarean section (CS) including elective caesarean section (ECS) and EmCS compared to WGP (16). CS and especially EmCS increase risk of complications to both mothers and children (10, 17). The risk of complication is likely to be higher in WLWH with impaired immune function (4). However with ART and the restoration of immune function it is possible that the previous shown risks of complications are no longer present.

This study aimed to compare known risk factors in pregnancy between WLWH and their matched controls. Further we examined if WLWH and their children are in greater risk of complications related to pregnancy and birth and whether the differences in complications could be explained by mode of delivery or risk factors during pregnancy.

Materials and Methods:

Study design and population

The study design and population is described in a previous study regarding mode of delivery (16). We conducted a retrospective matched cohort study including all WLWH giving birth to live born children in Denmark between 1 January 2002 and 31 December 2014. Exclusion criteria were HIV diagnosis after delivery, unknown mode of delivery or invalid Personal Identification Number (PIN), a unique 10-digit number assigned all Danish residents at birth or immigration. Only singleton pregnancies were included and every pregnancy was treated as a separate case. WLWH were divided in three groups due to a change in guidelines in 2007 where vaginal delivery was accepted in WLWH with VL < 1000 copies/mL (2002-2006, 2007-2008 and 2009-2014). Using the Danish Medical Birth Registry WLWH were individually matched at random 1:5 on maternal origin, age at delivery and parity to WGP. Women with unknown parity were set to be nulliparous. HIV characteristics on WLWH were extracted from medical records (16). Using the PIN, we linked to the following registries:

The Medical Birth Registry

In the Medical Birth Registry we retrieved information regarding date of birth, gestational age, birth weight and pregnancy- and birth-related complications.

The National Patient Registry

We used the National Patient Registry to extract all diagnoses regarding pregnancy, comorbidities and other risk factor during pregnancy, birth and complications to pregnancy or birth with the International Classification of Diseases, 10th revision (ICD-10) codes; DO0-999 and DZ3-399.

Statistics Denmark

From the registries at Statistics Denmark, we collected data on the maternal country of birth.

Outcomes

The primary outcomes of this study were risk factors during pregnancy comparing WLWH and WGP; including high body mass index (BMI >25), smoking, prior perinatal deaths, prior CS, viral hepatitis (chronic hepatitis B and C) and psychiatric disorders (DO993B1-5).

Secondary outcomes were pregnancy- or birth-related complications.

Pregnancy-related complications included: premature rupture of membranes (PROM, <37 weeks) and preterm premature rupture of membranes (PPROM, <37 weeks) due to the possibility of prolonged birth (>6 hours) and an subsequent risk of EmCS, intrauterine growth retardation (IUGR) or placental insufficiency (DO365A-E), gestational diabetes mellitus (GDM), hypertensive disorders (pre-eclampsia, eclampsia, hemolysis elevated liver enzymes low platelets syndrome (HELLP syndrome), preterm delivery (<37 weeks) and birth weight <2500 grams.

Birth related complications included amniotomy, failure to progress (DO62-639), indications of/and asphyxia (DO363+DO68-688), low Activity-Pulse-Grimace-Appearance-Respiration (APGAR) score, perineal laceration (2^{th} - 4^{th} degree or episiotomy), EmCS (DO821A-C), postpartum haemorrhage (>500 mL) and infections (DO86-DO869, i.e. all post-partum infections, including urinary tract infections, endometriosis, wound infections etc.).

Statistical analyses

Categorical variables were reported as counts and percentages and compared by chi-square test- or Fisher's exact test, as appropriate. Continuous variables were summarized as mean and 95% confidence intervals (CI) or median and interquartile range (IQR) and compared using Wilcoxon rank sum test.

Individual multivariate logistic regression was performed to identify differences in risk of complications. Odds ratios (ORs) and CI were estimated and adjusted *a priori*. Pregnancy related complications were adjusted for viral hepatitis, smoking, psychiatric disorders, age ≥30 years and parity. Low birth weight was additionally adjusted for prematurity. Birth related complications were adjusted for smoking, age ≥30 years, parity, previous CS, year and mode of delivery. Failure to progress, amniotomy and perineal lacerations were only assessed in women undergoing vaginal delivery. To control for repeated testing, a

combined *p*-value was estimated for variables spending more than one degree of freedom in the logistic regression. Individuals with missing explanatory values were excluded from the multivariate regression analyses. The validity of the model was tested using the Hosmer and Lemeshow Goodness-of-Fit Test. SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data analysis and *p*-values <0.05 (two-sided) were considered statistically significant.

Ethics

The project was approved by the Danish Data Protection (J.no. 2012-41-0904), the National Board of Health (J.no. 7-604-04-2/4) and the Danish Patient Safety Authority (case no. 3-3013-406/1-3). According to Danish law, approval from the National Committee on Health Research Ethics was not required as no biomedical interventions were performed.

Results

Baseline:

There were 406 HIV pregnancies resulting in live births in the study period, 17 were excluded due to either multiple pregnancies (n=6) or missing PIN (n=11) leaving 389 pregnancies in 304 WLWH for analysis. The pregnancies were matched to 1,945 singleton pregnancies in WGP. Baseline characteristics are listed in Table 1.

All WLWH were on ART at time of delivery; primarily on a combination regimen of 2 nucleoside reverse-transcriptase inhibitors and a protease inhibitor (PI) (73.8 %). The main PI's used were Ritonavir/Lopinavir (n=145, 37.3%) or Ritonavir/Atazanavir (n=71, 18,3%). At delivery 85.6 % of WLWH had HIV-RNA <40 copies/mL and 6 (1.5%) women had HIV-RNA >1000 copies/mL.

Risk factors present during pregnancy

WLWH presented with more risk factors than WGP during pregnancy: smoking (14.2 % vs. 7.5 %; *p*<0.0001), previous CS (36.7 % vs. 24.6 %; *p*=0.0001) and previous perinatal/neonatal death (3.9 % vs. 0.6 %; *p*=0.009). Furthermore, a larger proportion of WLWH had concomitant viral hepatitis (3.3 % vs. 0.6 %; *p*<0.0001) or a psychiatric

disorder (4.7 % vs. 2.6 %; *p*<0.02). Fewer WLWH had BMI >25 (32.9 % vs. 39.2 %; *p*<0.04). The comparison of risk factors present during pregnancy between WLWH and WGP is presented in Table 2.

Complications

Pregnancy related complications

As illustrated in Table 3, no significant differences were found between WLWH and WGP regarding GDM (3.6 % vs 3.7 %, aOR 1.0 (95%CI; 0.5-1.9) *p*=0.95), PROM/PPROM (8.0 % vs 6.3 %, aOR 1.2 (95%CI; 0.8-1.9) *p*=0.32), hypertensive disorders (1.8 % vs 3.7 %, aOR 0.6 (95%CI; 0.3-1.2) *p*=0.15), premature delivery (9.7 % vs 5.8 %, aOR 1.5 (95%CI; 0.9-2.2) *p*=0.09) or birth weight below 2500 grams (8.6 % vs 4.9 % aOR 1.3 (95%CI; 0.7-2.4) *p*=0.43). We did however; find more children with IUGR born to WLWH (5.5 % vs 3.1 %, aOR 1.9 (95%CI; 1.1-3.2) *p*=0.02).

During the study period the median gestational age of children born to WLWH increased almost reaching that of children born to WGP (2014: WLWH 39.1 weeks (IQR; 38.4-40.1 weeks) and WGP 39.9 weeks (IQR; 39.3-40.0) *p*=0.08). Accordingly, birth weights of children born to WLWH increased. However, measures were still lower than those of children born to WGP (2014: WLWH median 3,175.0 grams (IQR; 2,975.0-3,566.0) and WGP median 3,500.0 grams (IQR; 3,004.0-3,850.0) *p*=0.03) (Figure 1). When stratifying by mode of delivery, a significant difference was seen only in EmCS where children born to WLWH were both of smaller gestational age and of lower birth weight (Figure 1a-1c).

Birth related complications

WLWH were in increased risk of having an EmCS performed (26.0 % vs. 17.0 %, aOR 1.6 (95%CI; 1.2-2.1), *p*=0.0005) and postpartum hemorrhage (29.0 % vs. 25.7 % aOR 1.4 (95%CI; 1.0-1.9), *p*=0.02). Fewer children born to WLWH showed signs of asphyxia during birth (8.2 % vs 21.5 %, aOR 0.4 (95%CI; 0.2-0.6), *p*<0.0001). No significant differences regarding low APGAR scores or maternal infections were found (2.3 % vs 1.6 %, aOR 0.8 (95%CI; 0.4-1.8), *p*=0.64) and 2.4 % vs 2.3 %, aOR 0.9 (95%CI; 0.3-2.3), *p*=0.76).

In women delivering vaginally, there was no significant difference in risk of failure to progress or perineal lacerations, but fewer WLWH had amniotomies performed (3.8 % vs 17.1 %, aOR 0.2 (95%CI; 0.1-0.5) *p*=0.0003).

Discussion

In this nationwide cohort study including all WLWH in Denmark, who gave birth to singletons in the period 2002-2014, we found that WLWH had another risk profile during pregnancy, with increased rate of smokers, previous CS, concomitant viral hepatitis and psychiatric disorders. Despite this, we found no increased risk for most pregnancy- or birth related complications compared with WGP. However, our data suggest that WLWH are in higher risk of postpartum haemorrhage and placental insufficiency with more children born with IUGR. Further WLWH had almost twice the risk of EmCS subsequently having children with lower birth weight and smaller gestational age compared with WGP.

Pregnancy related complications

It is not well established whether HIV contributes to the development of diabetes mellitus (DM) (18). Some studies have found ART, especially PIs, to increase insulin resistance (19, 20), and other studies have shown a higher incidence of GDM in WLWH compared with WGP (6, 20). In our study, most women were treated with PI's during pregnancy and we did not find them to be in higher risk of GDM. This suggests that HIV and ART might not have the speculated impact on the GDM when adjusting for general risk factor. The lack of difference could be explained by the matching on age and origin and that the general incidence of GDM in Denmark is low, roughly estimated between 2-3% (21).

It has been speculated if WLWH are less likely to produce the excessive immune response normally seen in pre-eclampsia, and ART by restoring the immune function increases the risk (7). However recent studies have not been able to confirm this. We found both a low rate of hypertensive disorders including pre-eclampsia and no significant differences between groups. In comparison *Adams et al.* (22), reported that WLWH receiving ART were not at increased risk of pre-eclampsia and *Boyajian et al.* (13) found that fewer WLWH compared with WGP developed pre-eclampsia and only among WLWH with already established risk factors. Both studies pointed towards WLWH having lower risk of developing pre-eclampsia and ART not increasing the risk. Our data supports these

findings of a lower risk of developing hypertensive disorders in well-treated WLWH compared with WGP.

Children born by WLWH have previously been shown to have higher rates of low birth weight and prematurity (6, 11, 12). We did however not find significantly increased risk of premature delivery or low birth weights in WLWH in the adjusted analyses. The mechanisms to which HIV contributes to prematurity or low birth weight are not fully understood but it includes socioeconomic differences, HIV *per se*, ART and a general difference in risk factors during pregnancy (9, 23, 24). Since medical care, including ART, is tax-paid and provided free-of-charge to all people living with HIV in Denmark the contribution of socioeconomic issues to the results is presumably small compared with others (25). HIV has been suggested to cause intrauterine growth retardation as seen in other intrauterine viral infections such as cytomegalovirus (26) and *Ackerman et al.* (24) have posited that the viral infection of the placenta might lead to impaired maternal-fetal exchange or the maternal infection might disrupt normal placental implantation and development. In our cohort most WLWH were well treated with low HIV viral load. A viral infection of the placenta seems unlikely and the direct effect of HIV small.

Known risk factors to low birth weight or prematurity includes smoking and mental health (27, 28) Smoking causes vasoconstriction and placental insufficiency (29) and though the mechanism is not fully understood maternal mental stress and fetal growth seems to be associated (28). *Aliyu et al.* (26) found WLWH, that smoked during pregnancy, had an increased risk of low birth weight and prematurity compared to both HIV negative non-smokers and smokers, suggesting a possible synergistic intrauterine effect between smoking and HIV. In our cohort we found WLWH were twice as likely to smoke or suffer from psychiatric disorder during pregnancy compared to WGP. Both risk factors were included in the adjusted analysis and the variation could by a contributing factor to why previous studies have found increased risk of prematurity and low birth weight and why the difference was not found in our study.

Compared to WGP, children of WLWH had a smaller median gestational age and lower median birth weight ranging from 100-500 grams below WGP in recent years. This difference was most pronounced in WLWH delivering by EmCS and could be a result of some underlying obstetric- or pregnancy-related complication resulting in EmCS prior to

term, thus lowering the birth weight and gestational age. Previously WLWH were recommended ECS in week 38-39, in 2007 guidelines changed allowing more WLWH to deliver vaginally and the iatrogenic induced prematurity decreased. Correspondingly, the median gestational age increased during the study period, similar to other reported findings (6, 12, 30).

We did not have statistical power to examine the possible effects of ART or compare PI vs. non-PI regimens on outcomes. Recent studies have associated ART with prematurity and low birth weight (23, 31-33). In our study all WLWH were in ART at time of delivery and the vast majority received a PI regimen, and though we did not find increased risk of prematurity or births weight <2500g, we can not rule out that ART might be contributing to the lowered gestational age or smaller birth weight found in the study.

IUGR due to placental insufficiency is a major contributor to perinatal morbidity and mortality (34). WLWH in the present study had almost twice the risk of placental insufficiency and children with IUGR compared with WGP even after adjusting for smoking and viral hepatitis. These findings are supported by others who identified low maternal BMI and previous injection drug use to be more prevalent among IUGR-mothers (34). Unfortunately, we were not able to adjust for BMI due to a high number of missing values; however, we found a trend towards a lower BMI in WLWH. Though not investigating IUGR, *Canlorbe et al. (14)* found more WLWH having abnormal uterine Doppler results, increasing risks of placental insufficiency and IUGR. More research addressing IUGR and placental insufficiency is needed to understand a possible correlation.

Birth complications

WLWH have been thought to experience more complications to birth compared with WGP (4). Possible explanations include differences in mode of delivery where more WLWH deliver by ECS and a compromised immune system with increased vulnerability to infections (8). However with increasing experience in surgical techniques, anesthetic and prophylactic antibiotics some studies have declared elective caesarean section to be as safe as vaginal delivery (35). Further, WLWH, virally suppressed on ART with a stable CD4 count, would be expected to resemble WGP in risk. Correspondingly, we did not find WLWH at increased risk of postpartum infections.

The association between obstetric hemorrhage and HIV is not well established and studies are conflicting (7, 8). Studies have previously associated CS with a higher risk of postpartum blood loss (36). In a newer Danish study conducted in WGP, *Holm et al*. (36) found that ECS was associated with reduced risk of postpartum haemorrhage compared to intended vaginal delivery (36). Further the clinical estimates of blood loss during birth are uncertain and often based on estimates (36) and it s possible that if there are any complications i.e. EmCS, asphyxia etc. the estimate is higher than if the birth proceeds as planned. Though the analysis were adjusted for mode of delivery it is possible that in our cohort where more WLWH deliver by EmCS the result might be biased. Previous CS section are found to increase risk of postpartum bleeding (37) and as more WLWH have previously had a CS this might also contribute to the increased risk seen in our study.

In accordance with other studies (9, 12), we found WLWH in increased risk of EmCS compared with WGP. Predictors of EmCS have been investigated in a previous study (16) and included PROM, asphyxia, preterm delivery and delivery during evenings/nights. WLWH only have limited opportunity of vaginal delivery due to guidelines regarding assisted vaginal delivery, monitoring and rupture of membranes. As a consequence; WLWH delivering vaginally seem to be a selected group with a reduced risk of birth complications, since any sign of obstacles result in an EmCS. Children born to WLWH were less likely to develop signs of asphyxia and mothers undergoing vaginal delivery were less likely to fail to progress or get perineal lacerations. Correspondingly, *Azria et al.* (38) reported that WLWH without contraindications to vaginal delivery had the same birth outcomes as WGP and that WGP were more likely to have perineal lacerations. The same trend was seen in our study and could partly be explained by the lack of instrumental use in WLWH. Since guidelines recommend against amniotomies, significantly less WLWH had this procedure performed. An Italian multicentre study *Floridia et al.* (39) did not find invasive testing during pregnancy to increase risk of vertical transmission in well-treated women and *Cotter et al. (40)* did not find rupture of membranes beyond 4 hours to be a risk factor for transmission and a revision of guidelines could help in increasing the possibility and safety of vaginal delivery and reduce risk of EmCS and subsequent risk of other complications.

Strengths and limitations

Strengths of the present study include the nationwide design including all WLWH and individually matched controls with near complete information. Furthermore, we used national registries with prospectively collected data independently of outcome with minor risk of incorrect registrations (41). The retrospective design limits the study to rely on data extracted from chart reviews. The relative low number of pregnancies of WLWH was a limitation and the lack of statistical power to conduct analysis regarding associations between antiretroviral drugs and adverse outcomes.

Conclusion

WLWH had more risk factors present during pregnancy, similar risk of most pregnancy- and birth-related complications but a higher risk of postpartum haemorrhage and EmCS than WGP. Children born by WLWH had lower median birth weights and gestational age and were at higher risk of IUGR.

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All authors contributed substantially to the design of the study and in the acquisition of data. The data analysis was performed by MO together with KT and MH. MO, KT and AML drafted the manuscript. All authors critically revised, commented and approved the final manuscript.

Potential conflicts of interest

Outside the submitted work; KT has received research funding from Abbott and honoraria from Janssen-Cilag, Bristol-Myers Squibb and GlaxoSmithKline/Viiv. MH was supported by DNRF grant #126 and granted research funding from Gilead and honoraria from Bristol-Myers Squibb, Janssen and GlaxoSmithKline. TLK reports grants and personal fees from Gilead, Bristol-Myers Squibb, Merck Sharp Dohme, Jansen-Cilag, Glaxo-Smith Kline/Viiv. NW has received honoraria, given to her department, from Abbvie, Bristol-Myers Squibb, Merck Sharp Dohme, Gilead and Medivir. AML has received honoraria from Bristol-Myers Squibb, GlaxoSmithKline and Gilead. The other authors report no conflicts of interest.

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Table 1: Baseline characteristics and mode of delivery of women living with HIV (WLWH) compared with women from the general population (WGP) in Denmark 2002-2014

		WLWH (n= 389)	WGP (n= 1,945)	*p*-value[1]
Maternal characteristics				
Maternal age at delivery, (mean)(years) (95% CI)		32.7 (32.1-33.2)	32.5 (32.3-32.7)	0.50
African origin, n(%)		218 (56.0)	1,105 (56.8)	0.99
	missing	0	0	
Nulliparous, n(%)		148 (38.7)	715 (36.9)	0.01
	missing	(7)	(8)	
Birth characteristics				
Mode of delivery				
Vaginal delivery, n(%)		125 (32.1)	1,297 (66.7)	<0.0001
Assisted vaginal delivery, n(%)		5 (1.3)	129 (6.6)	
Elective caesarean section, n(%)		158 (40.6)	188 (9.7)	
Emergency caesarean section, n(%)		101 (26.0)	331 (17.0)	
missing		(0)	(0)	
Abnormal birth presentation, n(%)[2]		206 (53.6)	500 (26)	<0.0001
missing		(5)	(19)	
Gestational age, mean(weeks) (95%CI)		38.7 (38.5-39.9)	39.8 (39.7-39.9	<0.0001
missing		(0)	(0)	
Characteristics of children				
Sex, n(%)				
Male		218 (56.6)	1012 (52.0)	0.09
missing		(4)	(0)	

Fetal birth weight, mean (gram) (95% CI)	3191.8 (3132.4-3251.2)	3449.2 (3423.4-3474.9)	<0.0001
missing	(5)	(18)	
Maternal HIV characteristics			
Route of transmission, n(%)			
Sexual	273 (70.2)	-	
Injection drug use	11 (2.8)	-	
Other/missing	105 (27)	-	
HIV diagnosis during pregnancy, n(%)	71 (18.2)	-	
missing	(0)	-	
Time from diagnosis of HIV to delivery, median (years) (IQR)	6 (2.0-9.0)	-	
missing	(1)	-	
AIDS defining diagnose, n(%)	30 (8.0)	-	
missing	(16)	-	
CD4 cells at delivery, n(%)		-	
≥350 cells/µL	283 (75.9)	-	
200-349 cells/µL	68 (18.2)	-	
<200 cells/µL	22 (5.9)	-	
missing	(16)	-	
HIV RNA at delivery, n(%)			
<40 copies/mL	326 (85.6)	-	
40-999 copies/mL	49 (12.8)	-	
≥1000 copies/mL	6 (1.6)		
missing	(8)	-	
Time of ART initiation[3], n(%)			
Before pregnancy	247 (64.3)	-	
Before or at week 14	44 (11.4)	-	
After week 14	93 (24.2)	-	

missing	(5)	-
ART regimen at delivery[4], n(%)		
3 NRTIs	22 (5.7)	-
2 NRTIs + 1 NNRTI	46 (11.8)	-
2 NRTIs + PIs	287 (73.8)	-
Other	34 (8.7)	-
Missing	(0)	-
Mother to-child-transmission, n(%)	0 (0)	-

[1] The *p*-values were calculated without correction. The Kruskal-Wallis test was used for the continuous variables and the chi-square test was used for the categorical variables. [2]Abnormal presentation of fetus during birth: face, brow, breech and shoulder [3]ART, Antiretroviral Treatment; [4] NRTIs, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTIs, Non-Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; PI, Protease Inhibitors

	WLWH (n= 389)	WGP (n= 1,945)	*p*-value[1]

Table 2: Maternal risk factors for women living with HIV (WLWH) in Denmark 2002-2014 compared with women in the general population (WGP)

Smoking during pregnancy, n(%)			
No	315 (84.8)	1,761 (92.5)	<0.0001
Yes	52 (14.2)	143 (7.5)	
missing	(22)	(41)	
Previous caesarean section, n(%)[2]			
No	148 (63.3)	922 (75.5)	0.0001
Yes	86 (36.7)	300 (24.6)	
missing	(7)	(8)	
Previous perinatal or neonatal death, n(%)[2]			
No	225 (96.1)	1207 (98.8)	0.009
Yes	9 (3.9)	15 (1.2)	
missing	(7)	(8)	
Viral hepatitis[3], n(%)			
No	376 (96.7)	1,933 (99.4)	<0.0001
Yes	13 (3.3)	12 (0.6)	
missing	(0)	(0)	
Psychiatric disorders[4], n(%)			
No	362 (95.3)	1,876 (97.4)	0.02
Yes	18 (4.7)	50 (2.6)	
missing	(9)	(19)	
Body mass index >25, n(%)			
No	218 (67.1)	962 (60.9)	0.04
Yes	107 (32.9)	619 (39.2)	
missing	(64)	(364)	

[1] The *p*-values were calculated without correction. The χ^2 test or Fisher's exact test was used for the categorical variables. [2] The test was only performed in multiple parous women [3] Viral hepatitis: active and chronic hepatitis B and C. [4]Psychiatric disorders: schizophrenia, depression, anxiety, eating disorder, hyperkinetic disorders and others.

	WLWH (n=389)	WGP (n=1,945)	Unadjusted odds ratios	*p*-value	Adjusted odds ratios[1]	*p*-value
Gestational diabetes						
No	375 (96.4)	1,874 (96.4)	1	-	1	-
Yes	14 (3.6)	71 (3.7)	0.99 (0.6-1.8)	0.96	1.0 (0.5-1.9)	0.95
missing	(0)	(0)				
PPROM/PROM[2]						
No	358 (92.0)	1,822 (93.7)	1	-	1	-
Yes	31 (8.0)	123 (6.3)	1.3 (0.9-1.9)	0.23	1.2 (0.8-1.9)	0.32
missing	(0)	(0)				
Hypertensive disorders[3]						
No	373 (98.2)	1,855 (96.3)	1	-	1	-
Yes	7 (1.8)	71 (3.7)	0.5 (0.2-1.1)	0.07	0.6 (0.3-1.2)	0.15
missing	(9)	(19)				
Intrauterine growth retardation or placental insufficiency						
No	359 (94.5)	1,867 (96.9)	1	-	1	-
Yes	21 (5.5)	59 (3.1)	1.9 (1.1-3.1)	0.02	1.9 (1.1-3.2)	0.02
missing	(9)	(19)				
Premature birth (<37 weeks)						
No	346 (90.3)	1,832 (94.2)	1	-	1	-
Yes	37 (9.7)	113 (5.8)	1.7 (1.2-2.6)	0.006	1.5 (0.9-2.2)	0.09
missing	(6)	(0)				
Low fetal birth weight (<2,500g)						
No	351 (91.4)	1,833 (95.1)	1	-	1	-
Yes	33 (8.6)	94 (4.9)	1.8 (1.2-2.8)	0.004	1.3 (0.7-2.4)	0.43

Missing	(5)	(18)

Table 3: Unadjusted and adjusted odds ratios for pregnancy related complications in women living with HIV (WLWH) and women in the general population (WGP)

[1]Adjusted for viral hepatitis, smoking, psychiatric disorders, age ≥30 years and multi parity. [2]Adjusted for viral hepatitis, smoking, psychiatric disorders, age ≥30 years, multi parity and prematurity. The model is adjusted with HIV, comparing women with HIV to women of the general population regarding the different complications to pregnancy; the validity of the model was tested using the Hosmer and Lemeshow Goodness-of-Fit Test[2]. PPROM/PROM = Preterm premature rupture of membranes/Premature rupture of membranes; [3]Hypertensive disorders including pre-eclampsia, eclampsia and hemolysis elevated liver enzymes low platelets syndrome (HELLP syndrome).

Table 4: Unadjusted and adjusted odds ratios for birth related complications in women living with HIV (WLWH) and women in the general population (WGP)

	WLWH (n=389) n(%)	WGP (n=1,945) n(%)	Unadjusted odds ratios (95% CI)	*p*-value	Adjusted odds ratios[1] (95% CI)	*p*-value
Signs of asphyxia during birth						
No	357 (91.8)	1,527 (78.5)	1	-	1	-
Yes	32 (8.2)	418 (21.5)	0.33 (0.2-0.5)	<0.0001	0.4 (0.2-0.6)	<0.0001
missing	(0)	(0)				
Emergency caesarean section[2]						
No	288 (74.0)	1,614 (83.0)	1	-	1	-
Yes	101 (26.0)	331 (17.0)	1.7 (1.3-2.2)	<0.0001	1.6 (1.2-2.1)	0.0005
missing	(0)	(0)				
APGAR score at 5 minutes						
≥ 7	378 (97.7)	1,905 (98.4)	1	-	1	-
< 7	9 (2.3)	31 (1.6)	1.5 (0.7-3.1)	0.32	0.9 (0.3-2.3)	0.76
missing	(2)	(9)				
Postpartum bleeding						
No	276 (71)	1,446 (74.3)	1	-	1	-
Yes	113 (29.0)	499 (25.7)	1.2 (0.9-1.5)	0.17	1.4 (1.0-1.9)	0.02
missing	(0)	(0)				
Infections						
No	371 (97.6)	1,881 (97.7)	1	-	1	-
Yes	9 (2.4)	45 (2.3)	1.0 (0.5-2.1)	0.97	0.8 (0.4-1.8)	0.64
missing	(9)	(19)				

Unadjusted and adjusted odds ratios for birth related complications during vaginal deliveries in WLWH and WGP

	WLWH (n=130) n(%)	WGP (n=1,426) n(%)	Unadjusted odds ratios (95% CI)	*p*- value	Adjusted odds ratios [3] (95% CI)	*p*-value
Failure to progress						
No	98 (76.7)	1,025 (72.5)	1	-	1	-
Yes	30 (23.4)	389 (27.5)	0.8 (0.5-1.2)	0.32	0.9 (0.5-1.5)	0.73
missing	(2)	(12)				
Amniotomy						
No	125 (96.2)	1,182 (82.9)	1	-	1	-
Yes	5 (3.8)	244 (17.1)	0.2 (0.1-0.5)	0.0004	0.2 (0.1-0.5)	0.0003
missing	(0)	(0)				
Perineal laceration						
No	109 (85.2)	1,102 (77.9)	1	-	1	-
Yes	19 (14.8)	312 (22.1)	0.6 (0.4-1.0)	<0.0001	0.6 (0.4-1.1)	0.09
missing	(2)	(12)				

[1] Adjusted for mode of delivery, smoking, parity, previous caesarean section, age≥30 years and year of birth [2]adjusted for parity, smoking, previous caesarean section, age≥30 years and period of birth, [3]Adjusted for smoking, multiparity, previous caesarean section, age≥30 years and period of birth. The models are adjusted with HIV, comparing women with HIV to women of the general population regarding the different complications to birth. The validity of the models was tested using the Hosmer and Lemeshow Goodness-of-Fit Test.

Figure 1: Unadjusted ~~Overall~~ median birth weight and median gestational age in women living with HIV (WLWH) and women of the general population (WGP)

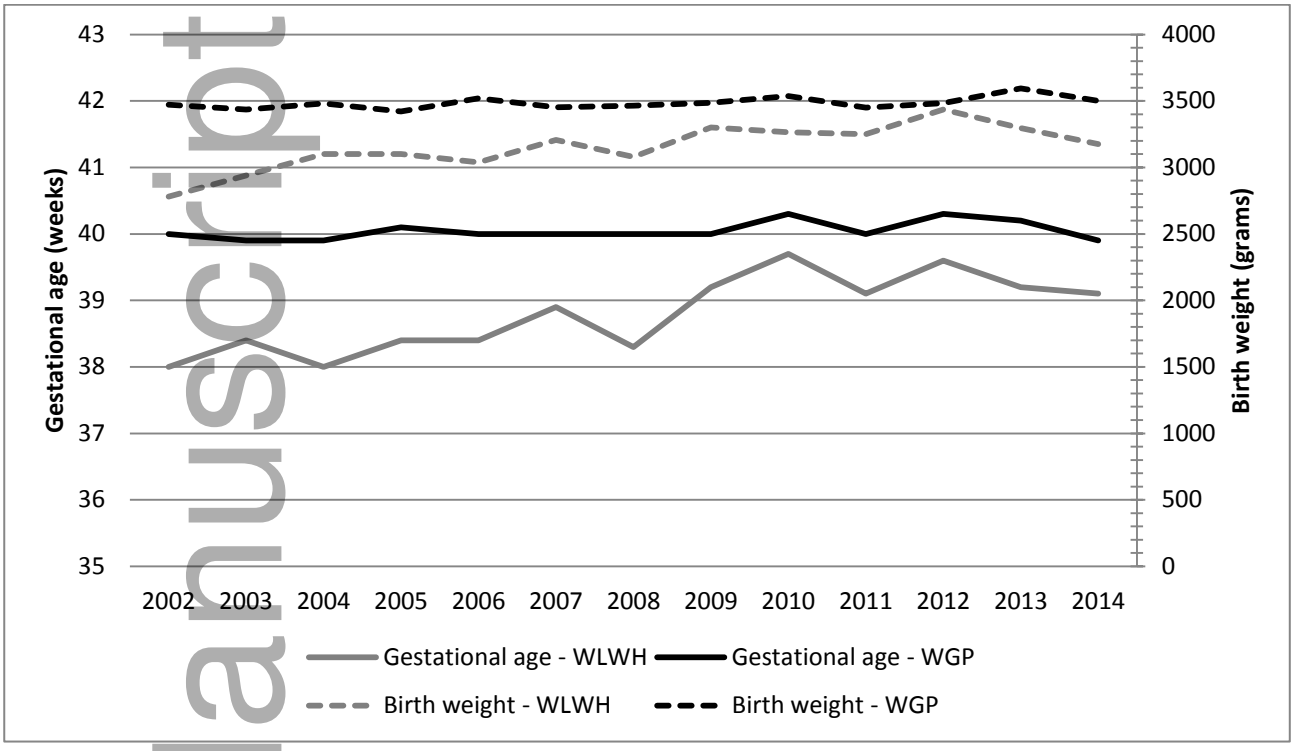

Figure 1a: Unadjusted m~~M~~edian birth weight and median gestational age in women living with HIV (WLWH) and women of the general population (WGP) delivering vaginally

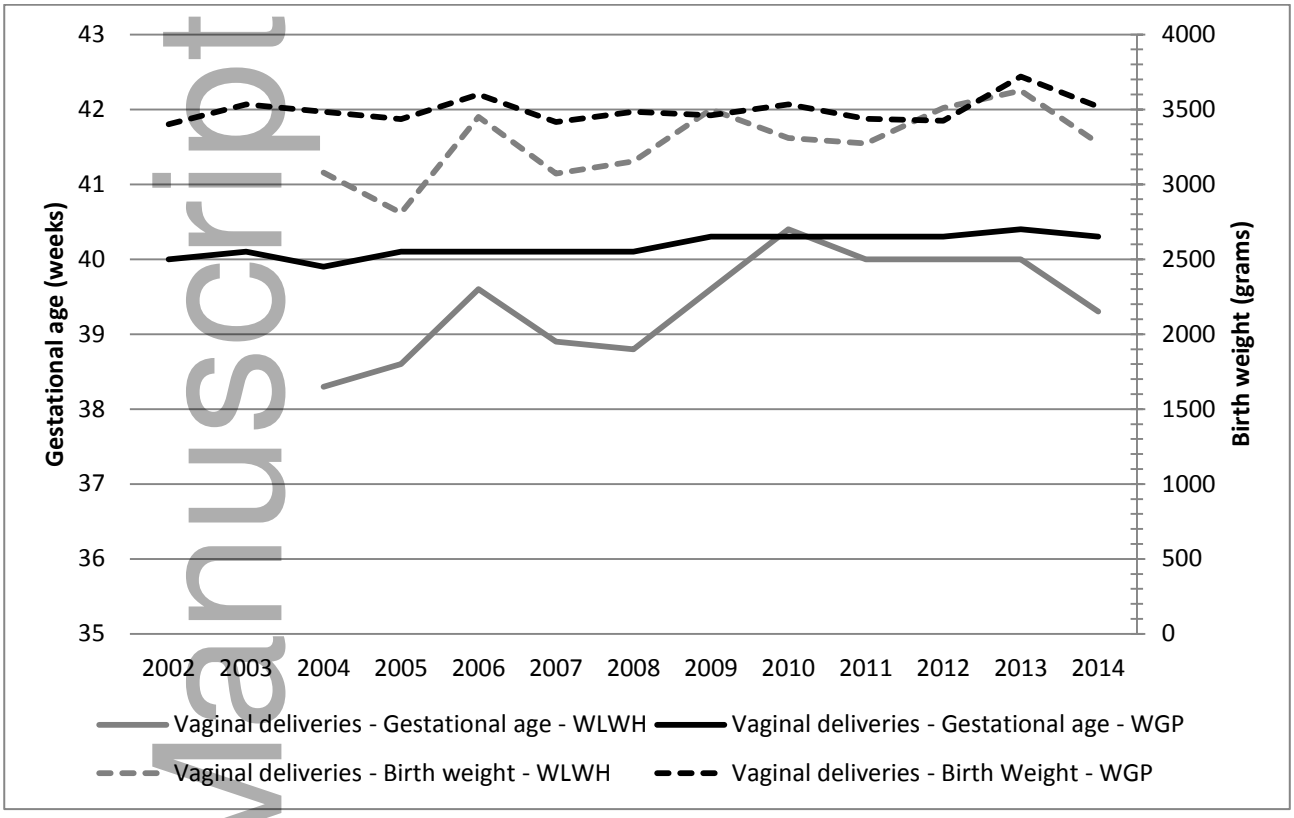

Figure 1b: Unadjusted m~~M~~edian birth weight and median gestational age in women living with HIV (WLWH) and women of the general population (WGP) delivery by elective caesarean section (ECS)

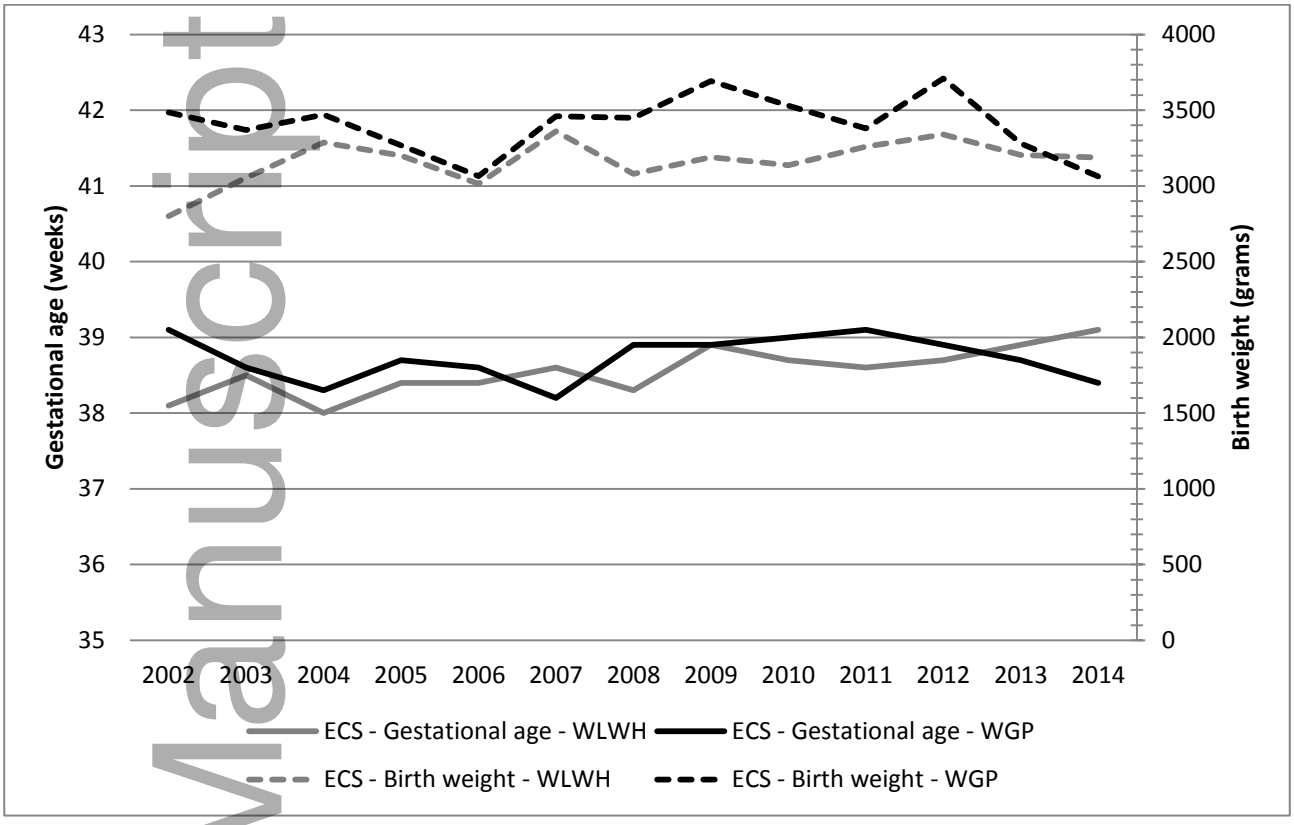

Figure 1c: Unadjusted ~~m~~Median birth weight and median gestational age in women living with HIV (WLWH) and women of the general population (WGP) delivery by emergency caesarean section (EmCS)