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Pregnancy outcomes among women with and without HIV infections who underwent excisional treatment for high-grade cervical intraepithelial neoplasia: a retrospective cohort study in low-resource settings

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ABSTRACT

Objective The standard treatment for high-grade squamous intraepithelial lesions is excisional involving the uterine cervix, while surveillance is an acceptable approach for low-grade squamous intraepithelial lesions. There is controversy about excisional treatment on pregnancy outcomes. The objective of this study was to determine pregnancy outcomes in women living with and without HIV who underwent excisional treatment for high-grade cervical intraepithelial lesions.

Design This retrospective cohort study compared the pregnancy outcomes of women with and without HIV who were or were not treated for cervical intraepithelial lesions. A cohort of 488 women with and without HIV infection who did or did not receive excisional treatment for cervical intraepithelial lesions between 2009 and 2022 was enrolled. Adverse pregnancy outcomes (preterm delivery and pregnancy loss) in women with and without HIV, untreated or treated for cervical dysplasia, were recorded and analysed. The significance of the obtained results was judged at the 5% level.

Study settings The study was conducted at all Academic Model Providing Access to Healthcare-Kenya satellite sites, which offer cervical cancer screening and treatment for cervical dysplasia in western Kenya. The Moi Teaching and Referral Hospital was also included.

Participants A cohort of 488 women aged between 20 years and 49 years, with and without HIV, diagnosed and treated for high-grade cervical intraepithelial neoplasia, and those followed up for low-grade cervical intraepithelial neoplasia between 2009 and 2022, were included.

Outcomes measured The study was interested in adverse pregnancy outcomes, particularly pregnancy loss and preterm delivery following cervical excision treatment for high-grade cervical intraepithelial lesions.

Results After adjustment for confounding factors, excisional treatment involving the uterine cervix—particularly cold knife conisation—was associated with higher odds of adverse pregnancy outcomes (OR 13.1; 95% CI 1.1 to 137.1; p=0.032). A prior history of adverse pregnancy outcomes was also strongly associated with subsequent adverse outcomes after treatment (OR 37.7; 95% CI 13.8 to 102.7; p<0.001). In contrast, maternal HIV infection was not independently associated with adverse pregnancy outcomes after adjustment (p=0.125).

Conclusion Adverse pregnancy outcomes after excisional treatment of the uterine cervix for high-grade squamous intraepithelial lesions are multifactorial and were associated with cold knife conisation and prior adverse pregnancy outcomes, while maternal HIV infection was not independently associated with adverse outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uses a multicentre design in low-resource settings.
⇒ A comparative method was applied between treated and untreated women.
⇒ HIV clinical data, such as viral load and CD4 count, were unavailable.
⇒ Pregnancy outcomes were based on self-reported information.
⇒ The retrospective design may have introduced recall bias.

INTRODUCTION

Cervical dysplasia and cancer continue to be major public health problems affecting middle-aged women, particularly in low- and middle-income countries (LMICs).[1] Globally, approximately 1–2% of women are diagnosed with high-grade cervical intraepithelial neoplasia (CIN 2+) each year.[2] However, this rate is reported to be higher than 10% in women with HIV infection. In sub-Saharan Africa, where human papillomavirus and HIV infections are endemic, the pooled prevalence of precancerous cervical lesions among

HIV-positive women is estimated to be >25.6%.[3] Owing to the close relationship between high-grade squamous intraepithelial lesions (HSIL) and HIV, cervical dysplasia is currently defined as an AIDS-related illness.

The WHO initiative for vaccination, screening and early treatment interventions to eliminate cervical cancer remains the gold standard for reducing morbidity and mortality from the disease.[4 5] This treatment for higher-grade CIN lesions involves removal or destruction of abnormal cervical cells by cryocautery, thermoablation, electrocautery, laser cautery, loop electrical excision procedure (LEEP) or cervical conisation, depending on the extent of the cervical precancerous lesion.[3 6 7] The management approach for patients with CIN is based on consensus guidelines and expert opinions, which consider the patient's age and desire for fertility, the grade of the disease and previous screening results.[8] Excisional treatment for cervical HSIL has had very positive results with a lower failure rate and recurrence. HIV-infected women have a higher risk of developing HSIL and cancer than women without HIV infection.[2] Thus, excisional treatment for cervical HSIL in HIV-infected women is most appropriate due to its lower failure rates and less recurrence.[8]

Excisional treatment for CIN may be associated with an increased risk of obstetric complications, including preterm delivery (PTD)[7] and second-trimester pregnancy losses (PLs). There is little evidence of an association between CIN and adverse pregnancy outcomes (APOs) in women with and without HIV infection. The evidence remains controversial in women without HIV infection, and there is a paucity of data on pregnancy outcomes among HIV-infected women who have undergone excisional treatment. We hypothesised that excisional treatment for high-grade CIN affects pregnancy outcomes more among HIV-infected women than among non-HIV-infected and untreated women. To fill this knowledge gap, we conducted a retrospective cohort study on women of reproductive age who had a confirmed histological diagnosis of CIN and received excisional treatment and/or follow-up (1) to determine the proportion of live births and APOs among women treated and untreated; (2) to determine the proportion of live birth in women with and without HIV infection treated; (3) to determine whether excisional treatment increases the risk of APOs; (4) to determine whether HIV infection increases the risk of APOs among women who undergo excisional treatment and (5) to determine the factors associated with APOs among the study population who underwent excisional treatment for CIN.

METHODS

Study design

This was a retrospective cohort study conducted on women of reproductive age (between 20 years and 49 years) who were diagnosed with and managed for CIN via the Academic Model Providing Access to Healthcare (AMPATH)-Kenya satellite sites in Western Kenya from January 2009 to January 2022. Data related to the diagnosis, management and HIV status were extracted from the AMPATH electronic registry for cervical cancer screening and treatment.

Data sources

Data on participant contact information, diagnosis, treatment modality and HIV status were extracted from the AMPATH-Kenya electronic database. HIV status was recorded at the time of cervical cancer screening. Women who tested HIV negative at screening underwent repeat HIV testing during their initial antenatal care visit, in line with routine testing for all pregnant women. Participants who tested HIV positive after treatment or diagnosis of CIN or during a subsequent pregnancy were classified as HIV-infected in this study.

Pregnancy-related data were obtained directly from the participants (self-reporting) as part of follow-up after diagnosis and treatment for CIN. The histological diagnosis evidence was obtained at the AMPATH satellite sites within the Rift Valley and Western Kenya, where screening for cervical cancer and treatment for cervical precancerous lesions have been implemented to reduce health disparities for the most preventable diseases, such as cervical cancer.

The screening and treatment programme for cervical cancer started in 2009 at Moi Teaching and Referral Hospital. Later, the screening programme was moved nearer the population at various facilities within the region. Since 2009, more than 1 00 000 women have been screened and treated for cervical dysplasia and cancer.

Study population

The study population comprises women diagnosed with cervical dysplasia, registered into the AMPATH electronic database of cervical cancer screening and treatment, who underwent excisional treatment for high-grade CIN or who were on follow-up without therapy for low-grade CIN as described in the 2018 National Cancer Screening and International Guidelines.[4 9] In this study, women younger than 25 years were included because local clinical protocols allow VIA screening below age 25 in the context of the high HIV prevalence. These younger participants had histologically confirmed CIN and therefore met the study inclusion criteria.

All women who received ablative therapy for CIN were excluded from this study because of a lack of post-treatment histological diagnosis. A separate study is currently underway to specifically evaluate pregnancy outcomes among women managed with ablative treatment.

Cervical cancer screening and diagnosis of CIN

Like in many other LMICs, visual inspection with acetic acid (VIA) is used as the primary cervical cancer screening method in low-resource settings. At AMPATH-Kenya satellite clinics, VIA is performed by trained registered

nurses with additional skills in cervical cancer screening and precancer treatment. VIA findings are recorded as negative (no acetowhite lesions) or positive (acetowhite lesions in the transformation zone). All VIA-positive women undergo colposcopic assessment, and colposcopically guided biopsies are taken from abnormal areas. Biopsy samples are processed and interpreted by qualified pathologists at an accredited pathology laboratory to establish a diagnosis of CIN.[10]

Treatment of CIN

Women diagnosed with low-grade CIN (CIN 1) are not treated but are placed on follow-up. At the same time, nurses and physicians offer those with cervical HSILs either ablative (cryotherapy or thermoablation) therapy. The following criteria are used for ablative treatment: lesions involving <75% of the transformation zone, CIN 2, lesions located entirely on the ectocervix, no endocervical canal or vaginal involvement by the lesion, no evidence of invasive cancer, non-pregnant women and women who do not menstruate.[11 12] For LEEP, standard criteria include CIN 2 and CIN 3, HIV infection, lesions involving ≥75% of the transformation zone, no endocervical canal or vaginal involvement by the lesion, no evidence of invasive cancer, non-pregnant women and women who do not menstruate.[13] Those with CIN 2 and CIN 3 lesions with endocervical canal extension or adenocarcinoma in situ (AIS) underwent cold knife conisation.[13 14]

This study included women of reproductive age between 20 years and 49 years (at the time of treatment) who were eligible to participate in this study, who gave verbal informed consent to participate in the study, who had an active mobile number, who conceived after diagnosis and treatment for CIN, and who had a histological diagnosis of low-grade or high-grade CIN. Women of reproductive age who were diagnosed with cervical dysplasia and who underwent ablative treatment were excluded from this study.

Sample size

Based on feasibility data from 2009 to 2022, more than 4385 women of reproductive age (4.4%) were diagnosed with and treated for cervical intraepithelial neoplasia. Of these, 2430 women were eligible for inclusion, while 1955 women who received ablative treatment were excluded. Using a cohort-based approach, approximately 488 participants reported at least one pregnancy outcome following the diagnosis and treatment of cervical intraepithelial neoplasia. The sample size calculation assumed that 50% of women were at risk of APOs and 50% were at low risk. Based on previous studies, the proportion of live births among treated women was estimated at 51%,[15] with the proportion of treated women estimated at 71%[15] and untreated women at 30%.[16] The desired statistical power was set at 0.84, with a two-sided type I error rate of 5% (critical value 1.96). Equal group sizes for treated and untreated women (1:1 ratio) were assumed, with further stratification by HIV status. Participants were recruited

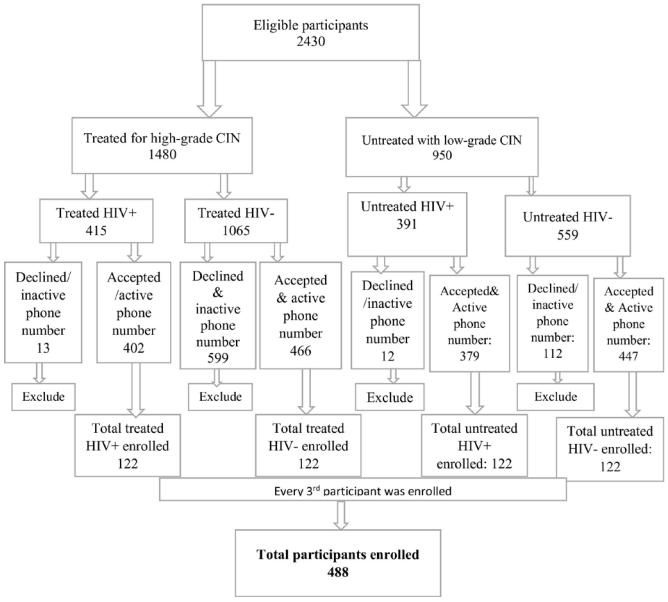

Figure 1 Study recruitment flow chart. CIN, cervical intraepithelial neoplasia.

using simple random sampling, as shown in figure 1. A larger proportion of eligible women without HIV declined participation or could not be reached because of inactive phone numbers (were excluded) in both the treated and untreated groups, compared with women with HIV, who are routinely engaged in regular clinical follow-up and care.

Study variables and outcomes of interest

Sociodemographic characteristics such as maternal age, marital status and education level were captured. In addition, maternal clinical characteristics, especially obstetric history before and after the diagnosis and treatment of CIN, a history of APOs defined by a history of PL (up to >28 weeks of gestation) and PTD, were recorded. In addition, data related to cervical cerclage were also captured. The gestational age (GA) (in weeks) at the time of delivery or at the time of loss, mode of delivery (vaginal vs caesarean section) and birth weight were also recorded for analysis. The HIV status of all participants was a variable of interest in the two groups of treated and untreated patients. CIN was graded as CIN 1, CIN 2, CIN 3 or AIS. These lesions were classified as low-grade intraepithelial neoplasia for CIN 1 and high-grade cervical intraepithelial neoplasia for CIN 2, CIN 3 and AIS. The participants were classified into two groups as showed in figure 1: women who received excisional treatment involving the uterine cervix and an untreated group, consisting of participants diagnosed with CIN 1. The procedures of interest included LEEP and cold knife conisation (CKC). The excisional thickness was classified as <1.0 cm and ≥1.0 cm according to Weinmann S and colleagues,[15] and data for those in whom the excisional thickness was not indicated were also captured and not included in bivariate analysis. For excisional thickness measurement, the local protocol uses

two excisions: superficial and deep excisions. The two were separately measured to calculate the sum.

The grade of the disease at the time of diagnosis, HIV status, excisional treatment and excisional thickness were identified as potential risk factors for adverse pregnancy outcomes. Using standard definitions, excisional treatment refers to LEEP and CKC; PL is defined as loss of the pregnancy before the age of viability (<28 weeks of gestation in low-resource settings); PTD is defined as delivery before 37 weeks gestational age (GA); adverse pregnancy outcomes (APOs) refer to PL and preterm delivery; nulliparous refers to a woman who has never given birth to a live child before diagnosis and treatment for CIN and grand-multiparous refers to a woman who has given birth to at least five live or stillborn babies at a gestational age of at least 28 weeks.

Clinical endpoint: live births after excisional treatment for high-grade CIN.

Composite endpoints

APOs (PL and PTD) after excisional treatment for high-grade CIN in women with and without HIV infection.

The conceptual framework (online supplemental figure 1) describes the relationships between the predisposing factors of APOs.

Statistical analysis

Data analysis was performed using the IBM SPSS software package V.20.0 (IBM, Armonk, New York, USA). Descriptive data are presented as frequencies and percentages for categorical variables, whereas means and SDs, medians and IQRs are presented as continuous variables. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. Categorical variables were compared via Fisher's exact test or the χ^2 test.

The pregnancy outcomes of women who received treatment, especially PL, PTD, live birth and term pregnancy, were compared with the outcomes of untreated women. A statistical analysis of the associations between APOs after diagnosis and excisional treatment in the two groups was performed, and the OR was calculated at a 95% CI for bivariate analysis. A subanalysis of the mode of delivery was also performed. An analysis of the associations between APOs and HIV infection status in women treated was also carried out.

In addition, the associations between APOs and treatment modality were analysed. Subanalyses of excisional treatment, types of excisional therapy and excisional thickness (<1.0 cm and ≥1.0 cm) were also carried out to determine any associations with APOs. Furthermore, factors that could be associated with APOs, such as maternal age, education level, disease severity, parity, pre-treatment history of APOs, cervical cerclage and HIV infection status, were also analysed.

Stratified analyses were used to compare the risk of APOs among women treated. ORs with 95% CIs were calculated. A multivariate logistic regression analysis adjusted the results and ORs for potential confounders.

Table 1

Variables	No.	%
Age (years)		
20–<30	86	17.6
30–<40	283	58.0
40–<50	119	24.4
Median (min–max)	35.50 (20.0–49.0)	
Marital status		
Single	109	22.3
Married	356	73.0
Divorced	10	2.0
Widowed	13	2.7
Education level		
Primary	161	33.0
Secondary	213	43.6
Tertiary	114	23.4

*Values are presented arenumber (percentage), unless otherwise stated. Age is additionally summarised using the median (minimum- maximum).
†IQR, Interquartile range; SD, Standard deviation

The significance of the obtained results was judged at the 5% level.

RESULTS

Baseline characteristics

Table 1 describes the sociodemographic characteristics of the participants. Most participants (58.0%) were between 31 and 40 years old.

Online supplemental table 1 presents maternal obstetric characteristics before treatment. Overall, 39.3% of participants had a history of APOs, and the majority were multiparous, including grand multiparous women (97.1%).

Online supplemental table 2 summarises clinical characteristics related to diagnosis and treatment. Most participants underwent loop electrosurgical excision procedure (95.5%), while 4.5% underwent CKC. Among women with documented excision depth, 53.2% had an excisional thickness of less than 1.0 cm, whereas 46.8% had an excisional thickness of 1.0 cm or greater.

Pregnancy outcomes after diagnosis and treatment

Table 2 presents pregnancy outcomes after diagnosis and treatment of CIN. The overall rate of APOs was 27.9%, with PL reported in 17.4% of participants and PTD in 10.5%.

Table 3 shows that the proportion of live births was lower among women who received excisional treatment compared with those who did not, irrespective of HIV status (77.4% vs 87.2%), and this difference was statistically significant (p<0.005). Overall, APOs occurred in 37.3% of the treated group compared with 18.4% in the

Table 2 Pregnancy outcomes after diagnosis and excisional treatment (n=488)

Variables	No.	%
Pregnancy outcomes		
Pregnancy loss (<28 weeks GA)	85	17.4
Preterm delivery (<37 weeks GA)	51	10.5
Term pregnancy (≥37 weeks GA)	352	72.1
Adverse pregnancy outcomes (pregnancy loss + preterm delivery)		
Yes	136	27.9
No	352	72.1
Live birth		
Yes	397	81.4
No	91	18.6
Intrauterine fetal demise		
Yes	6	1.2
No	482	98.8
Cervical cerclage		
Yes	27	5.5
No	461	94.5
Gestation at the time of delivery/loss (weeks)	**(n=488)**	
Mean±SD	35.72±7.45	
Median (min–max)	39.0 (3.0–41.0)	
IQR	38.0–39.0	
The mode of delivery		
Vaginal delivery	377	77.3
C-section	76	15.6
NA	35	7.1

C-section, Caesarean section; GA, gestational age; NA, not applicable.

untreated group. This difference was statistically significant. PL occurred more frequently in the treated group than in the untreated group (22.1% vs 12.7%; p<0.007). In addition, PTD frequently occurred in the treated group (15.2% vs 5.7%) than in the untreated group. This difference was statistically significant (p 0.001).

Table 4 summarises APOs among treated women with and without HIV infection. Among women treated for high-grade CIN, the proportion of live births was lower in women with HIV infection than in those without HIV (75.2% vs 79.5%), although this difference was not statistically significant (p=0.428). PL occurred in 23.8% of treated women with HIV compared with 20.5% of treated women without HIV, with no statistically significant difference (p=0.538). PTD was more frequent among treated women with HIV infection than among those without HIV (19.7% vs 10.7%); however, this difference did not reach statistical significance (p=0.053). In contrast, the proportion of term pregnancies was significantly lower among treated women with HIV infection compared with those without HIV (56.6% vs 68.9%; p<0.048).

As shown in table 5, 67.9% of women with HIV infection who received excisional therapy experienced APOs, while 86.8% of those without HIV infection who received excisional treatment experienced APOs. The differences were statistically significant (p=0.04). In the LEEP group, 90.6% of the participants with HIV infection experienced APOs, whereas all participants without HIV infection in the same group reported APOs. However, the difference was not statistically significant (p 0.99). In addition, 9.4% of women with HIV infection who had a CKC experienced adverse PL. In contrast, none of the women without HIV infection who received the same treatment had APOs. The difference was not statistically significant (p=0.99). 51.4% of women with HIV who underwent treatment and had an excisional thickness of <1.0 cm experienced APOs, whereas 69.7% of those without HIV infection experienced APOs. The differences were not statistically significant (p=0.12). Furthermore, 48.6% of participants with HIV infection who had an excisional thickness ≥1.0 cm experienced an APO, compared with 30.3% of participants without HIV infection. The differences were also not statistically significant (p 0.12).

Table 6 presents factors associated with APOs. Among women aged ≥40 years, 48.9% experienced APOs, compared with 17.5% who did not, corresponding to a 4.35-fold increased risk of APOs (p<0.001). APOs were also more common among women with HIV infection, occurring in 58.9% of HIV-positive women compared with 41.1% of HIV-negative women. Conversely, 55.2% of women without HIV infection did not experience APOs. HIV infection was associated with a 1.8-fold increased risk of APOs (p=0.034).

In the multivariable logistic regression analysis (table 7), treatment with excisional procedures (LEEP or CKC) was not independently associated with APOs (OR 1.1, 95% CI 0.01 to 92.2; p=0.965). However, treatment by CKC was significantly associated with increased odds of APOs compared with LEEP (OR 13.1, 95% CI 1.25 to 137.1; p=0.032).

Excision thickness ≥1.0 cm was not associated with APOs (OR 1.0, 95% CI 0.40 to 2.6; p=0.974). Maternal age >40 years was independently associated with higher odds of APOs (OR 2.7, 95% CI 1.05 to 7.1; p=0.039). Women with primary-level education had increased odds of APOs compared with those with secondary or tertiary education (OR 3.0, 95% CI 1.16 to 7.9; p=0.024).

Parity, history of cervical cerclage and HIV status were not significantly associated with APOs after adjustment. A history of APOs showed a strong independent association with subsequent APOs (OR 37.7, 95% CI 13.8 to 102.7; p<0.001).

Table 3 Associations between pregnancy outcomes after treatment in treated and untreated participants (n=488)

Variables	Treated (n=244)		Untreated* (n=244)		OR	P value
	No.	%	No.	%		
Live births (n=482)	(n=239)		(n=243)			
Yes	185	77.4	212	87.2	1.996	**0.005**
No*	**54**	**22.6**	**31**	**12.8**		
Adverse outcomes (pregnancy loss + preterm delivery)						
Yes	**91**	**37.3**	**45**	**18.4**	2.630	**<0.001†**
No*	153	62.7	199	81.6		
Type of adverse outcomes						
Pregnancy loss						
Yes	**54**	**22.1**	**31**	**12.7**	1.953	**0.007†**
No*	190	77.9	213	87.3		
Preterm delivery						
Yes	**37**	**15.2**	**14**	**5.7**	2.937	**0.001†**
No*	207	84.8	230	94.3		
Term pregnancy						
Yes	**153**	**62.7**	**199**	**81.6**	2.630	**<0.001†**
No*	91	37.3	45	18.4		
Cervical cerclage for second-trimester pregnancy loss (n=328)	(n=144)		(n=184)			
Yes	16	11.1	11	6.0	1.996	**0.098**
No*	128	88.9	173	94.0		
Gestational age at the time of delivery/loss						
Min–max	4.0–41.0		3.0–41.0		0.956	**0.001†**
Mean±SD	34.56±8.20		36.88±6.44			
The mode of delivery (n=453)	(n=218)		(n=235)			
Vaginal delivery*	167	76.6	210	89.4	2.565	**<0.001†**
Caesaren-section	51	23.4	25	10.6		

p: p-value for Odds ratio.
*Reference group.
†Statistically significant at p≤0.05.

DISCUSSION

This cervical cancer screening programme has significantly contributed to the early detection of cervical intraepithelial neoplasia, and fertility-sparing excisional treatment limited to the cervix for high-grade cervical lesions has helped women of reproductive age recover from disease progression and successfully complete pregnancies after treatment.

This study revealed that the proportion of live births in women who underwent excisional treatment involving the uterine cervix was lower in the treated group compared with the untreated group (77.4% vs 87.2%). In their study, Weinmann S and colleagues[15] reported a live birth rate of 51% in women who received excisional treatment involving the uterine cervix. The observed low birth rates are due to the increased risk of PL associated with excisional procedures in the uterine cervix.[15 17] However, PL in this context is multifactorial and includes disease factors such as HPV, high-grade CIN and HIV; maternal factors such as advanced maternal age and comorbidities and fetal factors such as chromosomal abnormalities. Several studies have been conducted in the field and have demonstrated the role of HPV infection and HSIL in causing APOs, such as PL and PTD.[18–23] Ambühl LM and colleagues reported that, in up to 24.9% of cases of abortion, 8.3% of the placental tissue samples from pregnant women were positive for HPV.[18] In 1997, Hermonat PL and colleagues reported higher rates of HPV-positive samples in spontaneously aborted products of conception than in elective abortions.[19] To date, these findings remain controversial.

Among women treated for high-grade cervical lesions, those with HIV infection had a slightly lower proportion of live births compared with HIV-negative women (75.2% vs 79.5%). However, the observed difference was not statistically significant (OR=1.28, p=0.428), indicating that HIV

Table 4 Associations between adverse pregnancy outcomes based on HIV infection status in women treated for high-grade CIN (n=244)

Variables	Treated HIV+(n=122)		Treated HIV− ® (n=122)		OR	P value
	No.	%	No.	%		
Live births (n=239)	(n=117)		(n=122)			
Yes	88	75.2	97	79.5	1.279	**0.428**
No®	**29**	**23.8**	25	20.5		
Adverse outcomes (pregnancy loss + preterm delivery)						
Yes	**53**	**43.4**	**38**	**31.1**	1.698	**0.048***
No®	69	56.6	84	68.9		
Type of outcomes:						
Pregnancy loss						
Yes	**29**	**23.8**	**25**	**20.5**	1.210	**0.538**
No®	93	76.2	97	79.5		
Preterm delivery						
Yes	**24**	**19.7**	**13**	**10.7**	**2.053**	**0.053**
No®	98	80.3	109	89.3		
Term pregnancy						
Yes	**69**	**56.6**	84	68.9	1.698	**0.048***
No®	53	43.4	38	31.1		
Women who received cervical cerclage (n=144)	(n=42)		(n=102)			
Yes	10	8.2	6	5.9	5.000	**0.004***
No®	32	26.2	96	94.1		
Gestational age at the time of delivery/loss						
Min–max	7.0–41.0		4.0–41.0		0.975	**0.111**
Mean±SD	33.71±8.24		35.40±8.11			
The mode of delivery (n=218)	(n=104)		(n=114)			
Vaginal delivery®	79	64.8	88	77.2	1.071	**0.830**
Caesarean-section	25	20.5	26	22.8		

® indicates the reference category
CIN, cervical intraepithelial neoplasia.

status was not associated with a significantly increased risk of APOs (PL or PTD) in this cohort. Although the numerical difference suggests a trend towards fewer live births in women with HIV infection, the lack of statistical significance implies that this finding may be due to chance rather than a true effect. To our knowledge, no studies have specifically evaluated live birth rates in women with HIV infection who underwent excisional treatment for high-grade cervical lesions. Nevertheless, the existing literature[24] consistently shows that HIV infection is associated with APOs, which may contribute to lower live birth rates even among treated individuals.[25 26]

APOs (PL or PTD) occurred more frequently in treated women with HIV (43.4%) than in treated women without HIV (31.1%). This difference was statistically significant (OR=1.70; p=0.048), indicating that women with HIV had 1.70 times higher odds (approximately 70% higher odds) of experiencing an adverse outcome compared with those without HIV. Although PL was slightly more common in treated women with HIV (23.8%) than in those without HIV (20.5%), this difference was not statistically significant (OR=1.21; p=0.538). Similarly, PTD occurred more often in treated women with HIV (19.7%) than in those without HIV (10.7%), but the difference did not reach statistical significance (OR=2.05; p=0.053). Comparable studies report PL and PTD rates among treated women of 25% and 14%, respectively.[15 27]

The higher rate of adverse outcomes observed in treated women with HIV may reflect underlying immunological or obstetric vulnerabilities associated with HIV infection, rather than the excisional procedure alone. HIV-related factors, including systemic inflammation, altered cervical remodelling[27] and higher obstetric risk profiles, are known to influence pregnancy outcomes independently of treatment and may therefore contribute to the increased odds observed in this cohort.

Table 5 Associations between adverse pregnancy outcomes and excisional treatment modalities in women with HIV infection versus women without HIV infection (n=91)

Variables	Adverse pregnancy outcomes in HIV+	Adverse pregnancy outcomes in HIV−®	OR	P value
Excisional treatment	(n=53)	(n=38)		
Yes	36 (67.9%)	33 (86.8%)	3.117	0.04*
No	17 (32.1%)	5 (13.2%)		
Excisional treatment:				
LEEP				
Yes	48 (90.6%)	38 (100.0%)	0.0	0.99
No	5 (9.4%)	0 (0.0%)		
CKC or cone biopsy				
Yes	5 (9.4%)	0 (0.0%)	0.0	0.99
No	48 (90.6%)	38 (100.0%)		
Excisional thickness:	n=37	n=33		
<1.0 cm				
Yes	19 (51.4%)	23 (69.7%)	2.179	0.12
No	18 (48.6%)	10 (30.3%)		
≥1.0 cm				
Yes	18 (48.6%)	10 (30.3%)	2.179	0.12
No	19 (51.4%)	23 (69.7%)		

LEEP, loop electrosurgical excision procedure
CKC, cold knife conisation; LEEP, loop electrosurgical excision procedure.

Furthermore, PL was more likely to occur in women with HIV infection treated for cervical high-grade intraepithelial lesions than in treated women without HIV infection (23.8% vs 11.5%). Elenga N and colleagues reported an overall PTD of 13.5% in HIV-uninfected women and 31.6% in HIV-infected women, and these findings are comparable.[27] The current study involved both HIV infection and treatment for CIN, while Elenga's study focused on HIV infection alone. Thus, the interpretation of the findings from the two studies should be done with caution. However, in the particular context of APOs and excisional treatment for CIN, the biological mechanism that leads to adverse reproductive outcomes in women receiving excisional treatment for CIN remains unclear.[28] Acquired mechanical weakness due to surgical excision and/or HSIL-induced inflammation[29] may be a logical hypothesis among others. This hypothesis is supported by previous studies by Gomez LM *et al* and Armbruster-Moraes E,[28] who reported the presence of High-risk human papillomavirus (HR-HPV) in the placental tissue and amniotic fluid of pregnant women who tested positive for HR-HPV and had a miscarriage.22–24 Therefore, HPV, HIV and HSIL cause inflammation of the placental tissue and lead to premature rupture of membranes and, consequently, PL or PTD. However, this remains controversial because several studies reported no association.[28–30] The major limitation of these studies that reported any association is the small number of participants.

Excisional treatment was more commonly associated with APOs among women with HIV than among women without HIV (67.9% vs 86.8%), and this difference was statistically significant (OR=3.12; p=0.04). This finding contrasts with that previously reported, no association between PL and excisional treatment involving the uterine cervix.[31–33] However, the study has similarities with those of previous studies that found associations between adverse obstetric outcomes and excisional treatment involving the uterine cervix.[27 34] This suggests that women with HIV who undergo excisional treatment may have a higher likelihood of experiencing adverse outcomes, although the underlying mechanism is uncertain. One possible explanation is that HIV-associated immunological changes and chronic inflammation may impair cervical healing following excision, potentially increasing susceptibility to cervical insufficiency or infection during pregnancy.

The type of excisional procedure (LEEP vs cone biopsy) was not significantly associated with APOs in either group, which may be attributable to limited variability, as nearly all women underwent LEEP. Excisional thickness (<1.0 cm vs ≥1.0 cm) was also not significantly associated with adverse outcomes, although a trend toward thicker excisions among HIV-positive women with adverse outcomes was observed. The absence of statistical significance is likely related to restricted sample size and insufficient power to detect excision-depth differences, a pattern reported in other studies where depth effects were present but highly dependent on sample size and procedural variability.[34 35]

Although the biological mechanism remains uncertain, cervical excision has been postulated to reduce cervical tensile strength and alter local tissue architecture, potentially contributing to pregnancy complications.[27] Changes in cervical healing, innate immunity and the vaginal microenvironment have similarly been proposed as contributing factors but require further investigation.[27] Evidence from previous studies has shown that larger or deeper excisions are more frequently associated with APOs than shallower ones, and that variability in excised volume may influence gestational duration.[15 32 35]

In this study, no statistically significant association was found between the grade of intraepithelial lesion and APOs among treated women. Unlike previous studies that reported higher rates of adverse outcomes in women with high-grade CIN,[7] our findings should be interpreted in the context of the comparator group used. All participants in this study had intraepithelial lesions, and the comparison was therefore between treated high-grade lesions and untreated low-grade lesions, rather than between women

Table 6 Factors associated with adverse pregnancy outcomes (n=244)

Variables	Adverse pregnancy outcomes in treated (n=90)		No-adverse pregnancy outcomes in treated (n=154)		OR	P value
	No.	%	No.	%		
Age (years)						
20–<30®	9	10.0	24	15.6	**1.000**	
30–<40	37	41.1	103	66.9	0.958	**0.921**
40–<50	44	48.9	27	17.5	4.346	**0.001***
Mean±SD	38.41±6.78		34.71±5.09		1.115	**<0.001***
Min–max	25.0–49.0		23.0–47.0			
Education level						
Primary	42	46.7	57	37.0	1.489	**0.139**
Secondary+tertiary®	48	53.3	97	63.0		
Grades of CIN						
LSIL (CIN 1) ®	0	0.0	0	0.0	–	–
HSIL (CIN2+CIN3+AIS)	90	100.0	154	100.0		
Parity before treatment						
Nulliparity®	3	3.3	3	1.9	1.736	**0.505**
Multiparity + grand parity	87	96.7	151	98.1		
History of cervical cerclage						
Yes	3	3.3	11	7.1	2.231	**0.228**
No®	87	96.7	143	92.9		
History of pregnancy adverse pregnancy outcomes						
Yes	79	87.8	32	20.8	27.381	**<0.001***
No®	11	12.2	122	79.2		
HIV status						
HIV positive	53	58.9	69	44.8	1.765	**0.034***
HIV negative®	37	41.1	85	55.2		

Bold values in tables indicate statistically significant associations (p < 0.5)
AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion.

with and without CIN. This limits the ability to determine whether CIN itself, independent of treatment, contributes to adverse outcomes. Other factors—including age, history of APOs and HIV status—were positively associated with adverse outcomes among treated women. This is consistent with the suggestion by Lycke *et al*[16] that CIN may carry a baseline risk of obstetric complications among affected women, although causation cannot be inferred from our data.

In the multivariate analysis, treatment type rather than excision itself was associated with APOs. Excisional treatment overall (combined LEEP and CKC) did not show an independent association with adverse outcomes (OR 1.1; 95% CI 0.01 to 92.2; p=0.965), whereas women who underwent CKC had significantly higher odds of adverse outcomes compared with those treated with LEEP (OR 13.1; 95% CI 1.25 to 137.1; p=0.032). These findings differ from those reported by Åström *et al*, who observed no increased obstetric risk following cervical excision,[34] but are consistent with studies demonstrating higher adverse outcome rates with larger or deeper excisions.[35–37] Variability in surgical technique, excision size and population characteristics may partly explain differences across studies. Cervical disease remains an important global public health issue, and a range of excisional modalities—including LEEP/large loop excision of the transformation zone (LETZ), CKC and CO_2 laser conisation—are used in the management of high-grade lesions. Recent evidence by Ferrari F *et al*[38] suggests that these techniques may differ in their clinical and pathological implications, including margin status, tissue preservation and reproductive outcomes. Accordingly, our findings should be interpreted within the broader context of evolving surgical approaches. As CO_2 laser conisation was not performed in this setting, direct comparison across all contemporary excisional methods was not possible.

Table 7 Logistic regression analysis

Variables	#Multivariate P value	OR (LL to UL 95% CI)
Excisional treatment (LEEP and CKC)		
Yes	**0.965**	1.1 (0.01 to 92.2)
No®	**1.000**	–
Treatment methods		
LEEP®	**1.000**	
CKC or cone biopsy	**0.032***	13.1 (1.25 to 137.1)
Indicate the excision thickness (n=173)		
<1.0 cm ®	**1.000**	
≥1.0 cm	**0.974**	1.0 (0.40 to 2.6)
Age (years)		
<40®	**1.000**	
>40	**0.039***	2.7 (1.05 to 7.1)
Education level		
Primary education	**0.024***	3.0 (1.16 to 7.9)
Secondary + tertiary®	**1.000**	
Grades of CIN		
LSIL (CIN 1)®	**1.000**	
HSIL (CIN2+CIN3+AIS)	–	–
Parity before treatment		
Nulliparity®	**1.000**	
Multiparity + grandparity	**0.776**	1.4 (0.14 to 13.5)
History of cervical cerclage		
No®	**1.000**	
Yes	**0.279**	0.4 (0.05 to 2.3)
History of pregnancy adverse pregnancy outcomes		
Yes	**<0.001***	37.7 (13.8 to 102.7)
No®	**1.000**	
HIV status		
HIV negative®	**1.000**	
HIV positive	**0.125**	2.2 (0.81 to 5.9)

AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; CKC, cold knife conisation; LEEP, loop electrosurgical excision procedure; LL, lower limit; LSIL, low-grade squamous intraepithelial lesion; UL, upper limit.

Excision thickness (≥1.0 cm) did not demonstrate a significant association with adverse outcomes in this cohort (OR 1.0; 95% CI 0.40 to 2.6; p=0.974), although previous research has suggested that deeper or larger excisions may increase obstetric risk.[15 32 35] This lack of association may be attributable to limited sample size or inadequate power to detect depth-related differences.

Several maternal characteristics demonstrated independent associations with adverse outcomes. Advanced maternal age (>40 years) was associated with a nearly threefold increase in adverse outcomes (OR 2.7; 95% CI 1.05 to 7.1; p=0.039), aligning with established evidence linking older age with placental dysfunction, chromosomal abnormalities and obstetric complications. A lower education level (primary education) was also associated with a threefold increase (OR 3.0; 95% CI 1.16 to 7.9; p=0.024), potentially reflecting socioeconomic disparities that influence access to antenatal care and health-seeking behaviour.

The strongest predictor in the model was a history of APOs, which increased the odds nearly 38-fold (OR 37.7; 95% CI 13.8 to 102.7; p<0.001). This finding is consistent with the literature showing recurrence due to underlying vascular, metabolic and infectious mechanisms.[37 39 40] Although HIV-positive status initially appeared to increase the risk (OR 2.1 in unadjusted analysis), the association was no longer statistically significant after adjustment (OR 2.2; 95% CI 0.81 to 5.9; p=0.125). This contrasts with pooled estimates from meta-analyses reporting higher risk in untreated populations with HIV,[26] suggesting that the relationship between HIV and pregnancy outcomes in women treated for CIN may be influenced by other clinical and demographic factors rather than HIV status alone.

This study is subject to limitations related to data collection and participant enrolment. Pregnancy outcomes were obtained through self-report rather than validated clinical records due to the absence of an integrated electronic system linking cervical screening and maternity services, which may have introduced recall bias or misclassification. Additionally, 612 eligible women in the treated group and 124 in the untreated group declined participation or could not be reached due to inactive phone contacts, and their outcomes were therefore not assessed. This loss to follow-up introduces the potential for selection bias if the characteristics or pregnancy outcomes of non-participants differ from those of participants. These limitations should be considered when interpreting the findings and highlight the need for prospective studies with systematically verified obstetric outcomes in similar settings. In addition, this study did not collect information on HPV vaccination status, despite strong evidence demonstrating the vaccine's safety and effectiveness in preventing high-grade cervical lesions. Recent large-scale data confirm the excellent safety profile of HPV vaccines, including no association with autoimmune diseases.[41] The absence of vaccination data in our cohort limits our ability to interpret cervical lesion patterns and reproductive outcomes within the full context of current cervical cancer prevention strategies.

The findings of this study are most applicable to women of reproductive age in low-resource settings, particularly in sub-Saharan Africa, where cervical cancer screening relies on VIA and HIV prevalence is high. The study reflects routine programme-based care, supporting

relevance to similar healthcare contexts. However, generalisability to high-income settings may be limited due to differences in screening strategies, treatment modalities, availability of excisional techniques and antenatal care systems. In addition, reliance on self-reported pregnancy outcomes and exclusion of women who underwent ablative treatment may further restrict extrapolation beyond comparable populations.

CONCLUSION

In conclusion, live birth rates and overall APOs did not differ significantly between women with and without HIV infection who underwent excisional treatment for high-grade cervical lesions, and HIV status was not an independent predictor after adjustment for confounding factors. Instead, adverse outcomes were associated with other clinical and sociodemographic characteristics, including CKC, advanced maternal age, a history of APOs and lower educational level, suggesting that the risk following excisional treatment is multifactorial rather than solely related to HIV infection. These findings support the need for cautious selection of excisional procedures, enhanced antenatal surveillance of high-risk women and tailored counselling in settings with high burdens of cervical precancer and HIV.

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