

Adverse Pregnancy Outcomes Following Cryotherapy, Thermal Ablation and Loop Electrosurgical Excision Procedure for Cervical Intraepithelial Neoplasia Treatment: A Pilot Study among Zambian Women

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Abstract

Background: Cervical Intraepithelial neoplasia treatments have become essential interventions to manage cervical lesions. Majority of the recipients of these treatments are women within the reproductive age group, who according to literature may be at risk of adverse pregnancy outcomes. This pilot study is part of a study investigating adverse pregnancy outcomes among women who received Cryotherapy, Thermal ablation and Loop Electrosurgical Excision Procedure compared to the untreated women in Zambia. **Materials and Methods:** This descriptive study analyzed records of 886 (n = 443 treated and n = 443 untreated) women aged 15 - 49 years. The women were either screened with Visual Inspection with Acetic Acid or treated for Cervical Intraepithelial neoplasia at the Adult Infectious Disease Centre between January 2010 and December 2020. Women meeting the criteria were identified using the Visual Inspection with Acetic Acid screening records and telephone interviews to obtain the adverse pregnancy outcome experienced. Data were analysed using STATA version 16 to determine the prevalence and obtain frequency distribution of outcomes of interest. Univariate and multivariable binary logistic regression estimated odds of adverse pregnancy outcomes across the three treatments. **Results:** The respondents were aged 15 to 49 years. Adverse pregnancy outcomes were observed to be more prevalent in the treatment group (18.5%) compared to the untreated group (5.4%). Nor-

mal pregnancy outcomes were lower in the treated (46.3%; n = 443) than the untreated (53.7%; n = 443). The treated group accounted for the majority of abortions (85.2%), prolonged labour (85.7%) and low birth weight (80%), whereas, the untreated accounted for the majority of still births (72.7%). Women treated with cryotherapy (aOR = 2.43, 95% CI = 1.32 - 4.49, p = 0.004), thermal ablation (aOR = 6.37, 95% CI = 0.99 - 41.2, p = 0.052) and Loop Electrosurgical Excision Procedure (aOR = 9.67, 95% CI = 2.17 - 43.1, p = 0.003) had two-, six- and ten-times higher odds of adverse pregnancy outcomes respectively, relative to women who required no treatment. **Conclusion:** Adverse pregnancy outcomes are prevalent among women who have received treatment in Zambia. The findings indicate that treating Cervical Intraepithelial Neoplasia has been linked to higher chances of experiencing abortion, delivering low birth weight babies and enduring prolonged labor that may result in a caesarean section delivery. Cervical neoplasia treatments, particularly Loop Electrosurgical Excision Procedure, are associated with significantly increased odds of adverse pregnancy outcomes. It is essential to include information about prior Cervical Intraepithelial neoplasia treatment outcomes in obstetric care.

Keywords

Adverse Pregnancy Outcomes, Cervical Intraepithelial Neoplasia, Cryotherapy, Thermal Ablation, Loop Electrosurgical Excision Procedure, Pilot, Reproductive Age

1. Background

Cervical Cancer is the leading cause of morbidity & mortality in Zambia [1] and the first most frequent cancer among women between 15 and 44 years of age [2]. For Low Middle Income Countries (LMICs), World Health Organization [3] [4] recommended using a “screen-and-treat” approach, in which Cervical intraepithelial neoplasia (CIN) grade 2 or 3 caused by Human Papilloma Virus (HPV) presumed to be precancerous after Visual inspection with Acetic Acid (VIA) can be treated with ablation or excision treatments. Ablative treatments include Cryotherapy, Thermal ablation, Laser Ablation, and radical diathermy while excisional treatments include laser conization, cold-knife conization (CKC) and Loop electrosurgical excision procedure (LEEP) [5]. Key treatments in Zambia since 2006 when Cervical Cancer Prevention Program in Zambia (CCPPZ) using VIA was introduced include Cryotherapy, Thermal ablation or LEEP [6] [7]. Treatments remove the transformation zone containing abnormal cells while cervical function is preserved [8]. These treatments have been reported to have negative impacts on maternal and neonatal outcomes [9] [10] [11].

Majority of the recipients of these treatments are women within the reproductive age group [12], who according to literature may be at risk of Adverse Pregnancy Outcomes (APOs) [13]. Major health implications of APOs can lead to

infant and maternal morbidities and mortalities [14]. APOs among infants may include preterm births, stillbirths, low birth weight, prolonged labour and caesarean section delivery; while maternal ones include long term physical and psychological problems [15]. These pregnancy outcomes after treatment remain a subject of concern. However, published studies and meta-analyses on the impact of CIN treatments provide contradictory conclusions and findings differ between studies [5] [16]. This has raised concerns for both health care providers and women who may be recommended for CIN treatment and still want to have children [10] [17]. The dearth of this critical information is the basis for conducting this study that aimed to investigate the APOs among women who received these treatments in Zambia.

2. Materials and Methods

This was a descriptive study conducted in 2023 using data from 2010 to 2020 records. A record review and a cross sectional approach were used to collect data from 886 (n = 443 treated and n = 443 untreated) women aged 15 - 49 years. The women were either screened with Visual Inspection with Acetic Acid or treated for Cervical Intraepithelial neoplasia at the Adult Infectious Disease Centre between January 2010 and December 2020. A total of 7000 treated women were eligible to participate in the study and only 4430 gave consent while 9000 untreated were interviewed with 4430 meeting the inclusion criteria. The sample size was calculated using Kelsey, Fleiss, Fleiss with continuity correction formula. Two data collection methods were used. Firstly, a data extraction sheet was used to collect records on socio demographic data, year of treatment, cervical VIA results, treatment method, contact details, HIV status, treatment type and post-screening clinical plan. Secondly, a structured questionnaire designed by the researcher was used to collect the APOs after CIN treatments. The questionnaire included both dichotomous (yes/no) and continuous variables. Trained interviewers obtained and clarified APOs via a telephone interview. Quota sampling was used to sample the records.

Women meeting the criteria in the treatment group were identified using the Visual Inspection with Acetic Acid screening records and telephone interviews to obtain conception details after VIA and CIN treatment. For the treated women, respondents were considered for study inclusion if they had conceived after any of the three CIN treatments. The first birth after the excision was utilized if a patient only underwent one treatment. If a patient had multiple treatments, the birth following the last procedure was used. The primary outcomes of interest for both the treated and untreated groups were abortion, prolonged labour that may lead to caesarean section delivery, low birth weight and stillbirth. The untreated respondents were selected if they gave birth following VIA screening. The data was directly entered onto an SPSS on a password protected laptop. In order to protect privacy, personal identifiers like participant names was omitted from the data set and replaced with a research number. Verbal con-

sent was obtained via a telephone interview, the respondents were informed on the purpose, their rights and what their participation involves. The process was documented and recorded. Only the women who agreed to participate in the study were interviewed. The information was confirmed, cleaned, and exported to STATA version 16 for statistical analysis. Descriptive statistics were used to determine the prevalence of APOs and obtain the frequency distribution in the study population. Univariate and multivariable binary logistic regression analyses were conducted to estimate the odds of experiencing APOs after CIN treatment, controlling for potential confounding variables. All tests were conducted at a 5% level of significance, and confidence intervals were set at 95%.

3. Results

Baseline characteristics

Most participants were aged 31 - 40 years 481 (54.3%; $n = 886$), and 20 - 30 years 208 (23.5%; $n = 886$) and the majority were in the same age groups (20 - 30 and 31 - 49) at delivery. Around half, (51.9%) of the participants attained tertiary level education, 387 (43.6%) and 356 (40.2%) were in the upper and lower middle economic class respectively (**Table 1**).

Prevalence of Adverse Pregnancy Outcomes

Overall, (12%; $n = 106$) of the participants experienced APOs while (88% $n = 780$) did not in both groups combined. Low birth weight (37.7%), prolonged labour (26.4%), and abortions (25.5%) accounted for the majority of outcomes among participants who reported adverse outcomes (**Figure 1**).

Table 1. Participants' socio-demographic characteristics ($n = 886$).

Characteristic	Levels	Frequency (n)	Percentage (%)
Age	<20 years	36	4.0
	20 - 30 years	208	23.5
	31 - 40 years	481	54.3
	41 - 50 years	161	18.2
Age at delivery	<20 years	30	3.4
	20 - 30 years	390	44.0
	31 - 40 years	380	42.9
	41 - 50 years	86	9.7
Level of education	Primary	167	18.9
	Secondary	259	29.2
	Tertiary	460	51.9
Socio-economic status	Upper middle	387	43.6
	Lower middle	356	40.2
	Other	143	16.1

Table 2 shows that APOs were more prevalent in the treatment group, (18.5%; n = 443) and (5.4%; n = 443) in the control group. Overall, half of the participants (50%; n = 443) received treatment, among which (48.1%; n = 443) received cryotherapy, (0.8%; n = 443) received thermal ablation and 10 (1.1%; n = 443) received LEEP. Considering only those who were treated, cryotherapy was the most common (96.1%; n = 443) from of treatment received ($p < 0.0001$). The proportion of APOs were significantly different across levels of treatment received ($p < 0.0001$) and across specific treatment received ($p = 0.046$).

Figure 2 shows that the treated group 205 (46.3%) experienced more APOs such as abortions (85.2%), prolonged labour (85.7%), low birth weight (80%). The normal outcomes were seen to be more in the untreated group 237(53.7%)

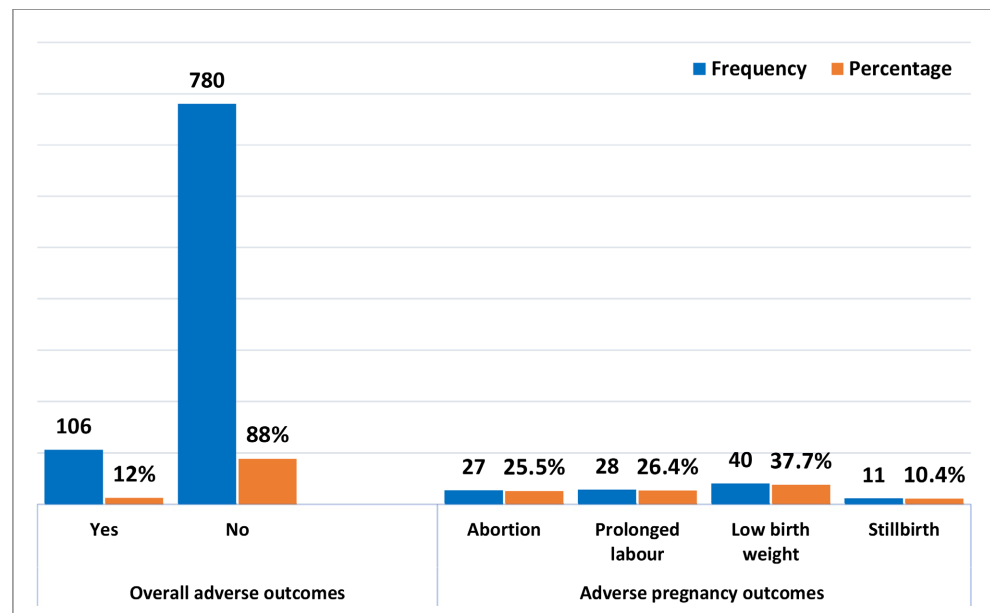


Figure 1. Overall prevalence of adverse pregnancy outcomes in both groups combined (n = 886).

Table 2. Adverse pregnancy outcomes across levels of treatment (n = 886).

Characteristic	Levels	Overall n (%)	Adverse pregnancy outcomes		p-value
			Yes, n (%)	No, n (%)	
Received treatment	No	443 (50.0)	24 (5.4)	419 (94.6)	<0.0001 ^{CH}
	Yes	443 (50.0)	82 (18.5)	361 (81.5)	
Treatment received	None	443 (50.0)	24 (5.4)	419 (94.6)	<0.0001 ^{FE}
	Cryotherapy	426 (48.1)	75 (17.6)	351 (82.4)	
	Thermal ablation	7 (0.8)	3 (42.7)	4 (57.1)	
	LEEP	10 (1.1)	4 (40.0)	6 (60.0)	
Specific treatment received	Cryotherapy	426 (96.1)	75 (17.6)	351 (82.4)	0.046 ^{FE}
	Thermal ablation	7 (1.6)	3 (42.9)	4 (57.1)	
	LEEP	10 (2.3)	4 (40.0)	6 (60.0)	

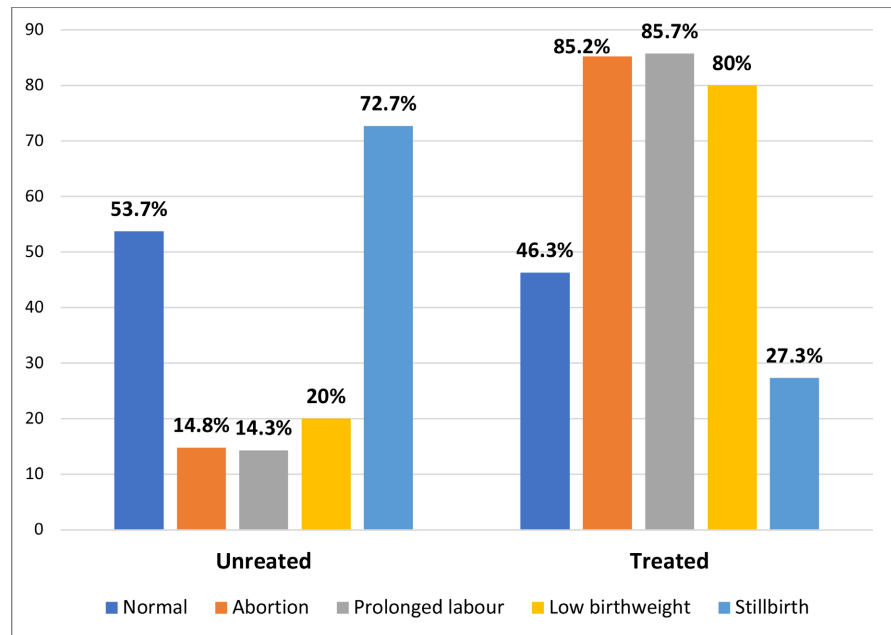


Figure 2. Adverse pregnancy outcomes between the two groups (n = 886).

however, the untreated group accounted for the majority of stillbirths (72.7%).

Overall, both unadjusted and adjusted analysis showed that, women treated with cryotherapy, thermal ablation or LEEP had significantly increased odds of APOs compared to those who required no treatment. Adjusted analysis show that women treated with cryotherapy (aOR = 2.43, 95% CI = 1.32 - 4.49, p = 0.004), thermal ablation (aOR = 6.37, 95% CI = 0.99 - 41.2, p = 0.052) and LEEP (aOR = 9.67, 95% CI = 2.17 - 43.1, p = 0.003) had two-, six- and ten-times higher odds of APOs respectively, relative to women who required no treatment.

4. Discussion

This study is part of the study that sought to investigate the APOs among women who received CIN using cryotherapy, thermal ablation and LEEP treatment in Zambia. The study has shown that APOs are prevalent among women who have received CIN treatment. Furthermore, the study has linked CIN treatment to higher chances of experiencing abortion, delivering low birth weight babies and enduring prolonged labor that may result in a caesarean section delivery. However, Stillbirths were more prevalent among the untreated women. CIN treatments, particularly Loop Electrosurgical Excision Procedure, are associated with significantly increased odds of adverse pregnancy outcomes. Majority of APOs were among women aged 20 - 49 years. This finding compares well with the findings in Zambia and Nigeria that found women between 15 and 49 years to be at risk of HPV and CIN [1] [18]. Approximately 51.9% of the participants achieved a secondary level of education, the CIN screening and treatment in this group could potentially be linked to the education provided in schools during HPV vaccination campaigns. Roughly 43.6% and 40.2% belonged to the upper and lower middle economic class, respectively. This may be linked to the fact that

women within these income brackets often possess the financial means to make cervical cancer screening and treatment more accessible.

The overall prevalence of APOs in the both groups was 12% (**Figure 1**), indicating that APOs may be experienced by both the treated and untreated clients. Specifically, 18.5% of the treated group experienced APOs, whereas only 5.4% of untreated group had such outcomes (**Table 2**). The prevalence of normal pregnancy outcomes was found to be lower in the treated than the untreated. The higher prevalence of APOs in the treatment group compared to the untreated group suggests that CIN treatment may have a detrimental effect on subsequent pregnancies. Abortions (85.2%), prolonged labour (85.7%) and low birth weight (80%) were the most prevalent APOs among the treated compared to the untreated group that accounted for the majority of still births (72.7%) [**Figure 2**].

The finding that abortions were more prevalent after CIN treatment is similar to that of Sun *et al.*, 2022 & Weinmann *et al.*, 2017 [19] [20] that observed an association between pregnancy loss and ablative surgical treatment and suggested further investigation. Similarly, the finding that low birth weight was a significant adverse outcome aligns with previous studies examining the impact of CIN treatment on pregnancy outcomes [21] [22]. The association between CIN treatment and low birth weight can be attributed to potential cervical insufficiency resulting from the removal of cervical tissue during treatment procedures, which may compromise the structural integrity of the cervix and contribute to premature birth.

Prolonged labor was another notable adverse pregnancy outcome observed in this study. A plausible explanation for this could be the disruption of cervical tissue and potential scarring resulting from CIN treatment procedures may affect cervical dilation, leading to difficulties in the progress of labor. This finding is similar to previous research that reported an increased risk of labor complications, including prolonged labor, following CIN treatment [10] [16]. The study further highlight that the specific treatment received for CIN significantly influenced the proportion of APOs. This finding corroborates with previous studies that revealed that treatment modalities, such as cryotherapy, thermal ablation, LEEP may have varying effects on cervical integrity and subsequent pregnancy outcomes [5] [16] [17].

Cryotherapy emerged as the predominant therapy, possibly attributed to its status as the longest-standing treatment for precancerous lesions in Zambia since its introduction in 2006. Based on adjusted analysis, women treated with cryotherapy had two times higher odds of APOs compared to women who required no treatment. Similarly, women treated with thermal ablation had six times higher odds, while those treated with LEEP had ten times higher odds (**Table 3**). The increase in odds has been echoed in other studies by Jakobsson *et al.*, [23] & Papoutsis *et al.*, [24], which revealed that LEEP compared to thermal ablation and Cryotherapy had higher rates of adverse outcomes even after adjusting for confounders [25]. These findings indicate that the choice of treatment modality for CIN may have implications for subsequent pregnancies and should

Table 3. Logistic regression analysis on effect of treatment on pregnancy outcomes.

Variable Treatment	Crude estimates			Adjusted estimates		
	cOR	95% CI	p-value	aOR	95% CI	p-value
None	Ref			Ref		
Cryotherapy	3.73	2.31 - 6.03	<0.0001	2.43	1.32 - 4.49	0.004
Thermal ablation	13.09	2.77 - 61.8	0.001	6.37	0.99 - 41.2	0.052
LEEP	11.64	3.01 - 44.0	<0.0001	9.67	2.17 - 43.1	0.003

cOR = Crude Odds Ratio, aOR = adjusted Odds Ratio, CI = Confidence Interval.

be carefully considered. Caution should be exercised while performing excisional therapy on women who are of reproductive age.

There are some limitations to consider in this study. Firstly, data collection was reliant on self-reported interviews, potentially leading to recall bias. Secondly, the relatively small sample size might have affected the statistical power and the ability to generalize our findings. Thirdly, the scope of the study was confined to examining abortion, low birth weight, prolonged labor, and stillbirth as the outcomes of interest. Despite all these, the study demonstrated the effect of CIN treatments on APOs in Zambia. Furthermore, the research introduced a novel aspect of abortion outcomes that has received comparatively limited attention in prior studies.

5. Conclusion

Overall, these findings of an ongoing study indicate that APOs are more prevalent among women who have received CIN treatment. Treating CIN has been linked to higher chances of experiencing abortion, delivering low birth weight babies and enduring prolonged labor that may result in a caesarean section compared to pregnant women who don't receive treatment. CIN treatments, particularly Loop Electrosurgical Excision Procedure, are associated with significantly increased odds of adverse pregnancy outcomes. It may be essential for healthcare providers in future to include information about prior CIN treatment outcomes in obstetric care for women to make informed decision.

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Ethical Considerations

Ethical approval was granted by the University of Zambia, Biomedical Research Ethics Committee (REF. No. 3185-2022) and written permission was sought from the National Health Research Authority (NHRAR-R-1341/08/11/2022).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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