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Adverse Pregnancy Outcomes Following Cryotherapy, Thermal Ablation, and Loop Electrosurgical Excision Procedure for Cervical Treatments among Reproductive Age Women in Zambia

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Abstract

Background: Cervical Intraepithelial neoplasia treatments have become essential interventions to manage cervical lesions. Most recipients are women of reproductive age who, as reported in the literature, may be at risk of adverse pregnancy outcomes. This study investigated the risk of abortions, prematurity, stillbirths, and prolonged labor among reproductive-age women following Cryotherapy, Thermal ablation, and Loop Electrosurgical Excision Procedure treatments in Zambia. **Methods:** This cross-sectional study analyzed records of 8000 women aged 15 - 49 years at the Adult Infectious Disease Control Centre using records between January 2010 and December 2020. Women constituting the treatment group were all respondents treated by cryotherapy, thermal ablation, and LEEP, while the control group were VIA negative women. Women from both groups were invited to answer a phone survey. Data were analyzed using Stata version 16; descriptive analysis estimated the prevalence and obtained the frequency distribution of abortion, prematurity, prolonged labor and fresh stillbiths. Chi-square and Fisher's exact test established the associations of CIN and APOs at 95% Confidence intervals. Univariate and multivariable binary logistic regression estimated the odds of adverse pregnancy outcomes across the three treatments. **Results:** Adverse pregnancy outcomes were more prevalent in the treatment group (39.2%) compared to the untreated group (16.9%). Across the two groups, normal outcomes were lower in the

treated (42.3% vs 57.7%). The treated group accounted for the majority of abortions (74.5% vs 25.5%) and prolonged labor (72.5% vs 27.5%), while the untreated group accounted for higher proportions of stillbirths (66.7% vs 33.3%) and prematurity (53% vs 47%). Adverse pregnancy outcomes were five and two times more likely in women treated with thermal ablation (aOR = 5.05, 95% CI = 4.01 - 6.36, p < 0.0001) and Loop Electrosurgical Excision Procedure (aOR = 2.73, 95% CI = 2.20 - 3.40, p < 0.0001), respectively. **Conclusion:** Cervical treatment among Zambian women increases the risk of abortion and prolongs labor. Therefore, caution should be taken when administered to those of reproductive age. Vigilant monitoring should be maintained during pregnancy, delivery, and postpartum to improve maternal and neonatal health.

Keywords

Adverse Pregnancy Outcomes, Cervical Treatment, Cryotherapy, Thermal Ablation, Loop Electrosurgical Excision Procedure, Reproductive Age Women, Zambia

1. Background

Cervical intraepithelial neoplasia (CIN) refers to precancerous lesions in the cervical cells, which, if left untreated, can progress to cervical cancer [1]. Effective treatments for the management of CIN are crucial, as cervical cancer is the fourth cause of cancer-related death among women worldwide [2]. In Zambia, it accounts for 23% of all cancer cases and remains a leading cause of morbidity and mortality [3] [4]. The Cervical Cancer Elimination Initiative has established national 90-70-90 goals for countries aiming to eliminate cervical cancer by 2030. These goals include ensuring that 90% of girls are fully vaccinated with the Human Papiloma Virus (HPV) vaccine by age 15, 70% of women undergo screening with a high-quality test at ages 35 and 45, and 90% of women with precancerous lesions or invasive cancer receive appropriate treatment [2]. This has been achieved mainly through the "screen-and-treat" approach, where CIN grade 2 or 3 lesions, often identified through visual inspection with acetic acid (VIA) and presumed to be precancerous, are treated with ablation or excision treatments [5]. The treatments used in Zambia include Cryotherapy, Thermal ablation, and Loop electrosurgical excision procedure (LEEP). The therapy aims to remove the transformation zone (TZ) of the cervix containing pre-cancerous lesions; however, this procedure has, in some studies, been reported to increase the risk of adverse pregnancy outcomes (APOs), which potentially affect maternal and neonatal health [6]. This has led to concerns among women of reproductive age undergoing CIN treatment in Zambia, many of whom have reported experiencing APOs following the procedure. APOs are birth outcomes other than normal pregnancy outcomes and include but are not limited to low birth weight, stillbirth, prematurity, preeclampsia, hypertensive disorders, gestational diabetes, and prolonged labor [7].

While studies have investigated APOs being prevalent and exerting a notable impact on both maternal and neonatal morbidity and mortality rates in Zambia [8], few have directly examined their relationship with CIN treatment, the available studies have provided conflicting findings across different regions and studies [9] [10]. This current study was essential because APOs in Zambia and elsewhere already represent a significant concern [8]. Utilizing treatments that may impact the APOs may worsen the APOs already existing among reproductive-age women. The outcomes of interest in our study were abortion, prematurity, fresh stillbirth, and prolonged labor. No local studies in Zambia have directly explored the connection between CIN treatment and APOs. This lack of clarity had resulted in confusion among healthcare providers and women considering CIN treatment who still wish to maintain their fertility [11] [12]. This study aimed to investigate the APOs among women of reproductive age across Cryotherapy, thermal ablation and LEEP treatments.

2. Materials and Methods

This cross-sectional study analyzed records of 8000 women aged 15 - 49 years using records between January 2010 and December 2020 at the Adult Infectious Disease Control Centre (AIDC). Data collection took place between February 2023 and August 2023 using records of VIA screening and CIN treatment register of women seen at the nurse led "see-and-screen" outpatient department. Women constituting the treatment group were all respondents treated by cryotherapy, thermal ablation and LEEP, while the control group were untreated HPV negative women. Women from both groups were invited to answer a phone survey (**Figure 1**). Data was extracted from the records by five nurses who were familialized with the VIA screening and treatment and electronic health system of the AIDC. Interviews were led by the researcher who is an oncology nurse and 14 oncology nurses trained in cervical cancer screening based on a questionnaire structured along the following sections: 1) update of cervical cancer screening and treatment 2) obstetric history prior to screening and 3) obstetric history since CIN treatment. Socio-demographic data, previous screening results and treatment received, HIV status and smoking status were retrieved from the records. The tool was adapted from the 13 core outcome sets (COS) relevant to the women's and newborn health CROWN database and other reviewed literature [13]. Additionally, the questionnaire was further adapted after being pretested on 10% of the respondents (Mwiinga-Kalusopa *et al.*, 2024). Respondents who did not answer their phones on the first attempt were called again at least twice at different times of the day or week. If no answer was received after two tries, the next of kin indicated by the participant as additional contact was called to update the participants contact information. The questionnaire included both dichotomous (yes/no) and continuous variables. The University of Zambia, Biomedical Research Ethics Committee (REF. No. 3185-2022) granted ethical approval, and written permission was sought from the National Health Research Authority (NHRAR-R-

1341/08/11/2022) to conduct the study. All respondents provided informed oral consent over the phone to participate in the study, the first birth after the excision was utilized if a patient only underwent one treatment while the birth following the last procedure was used if a patient had multiple treatments. The outcomes of interest included abortion, prematurity, stillbirth, and prolonged labor. Operational definitions used in the study were: Abortion: The termination of pregnancy, spontaneous or induced, before 28 weeks of gestation. Prematurity: a baby born alive after 28 weeks before 37 weeks of pregnancy. Stillbirth: delivering a fresh stillbirth after 28 weeks gestation. Prolonged labor: Labor longer than 18 hours.

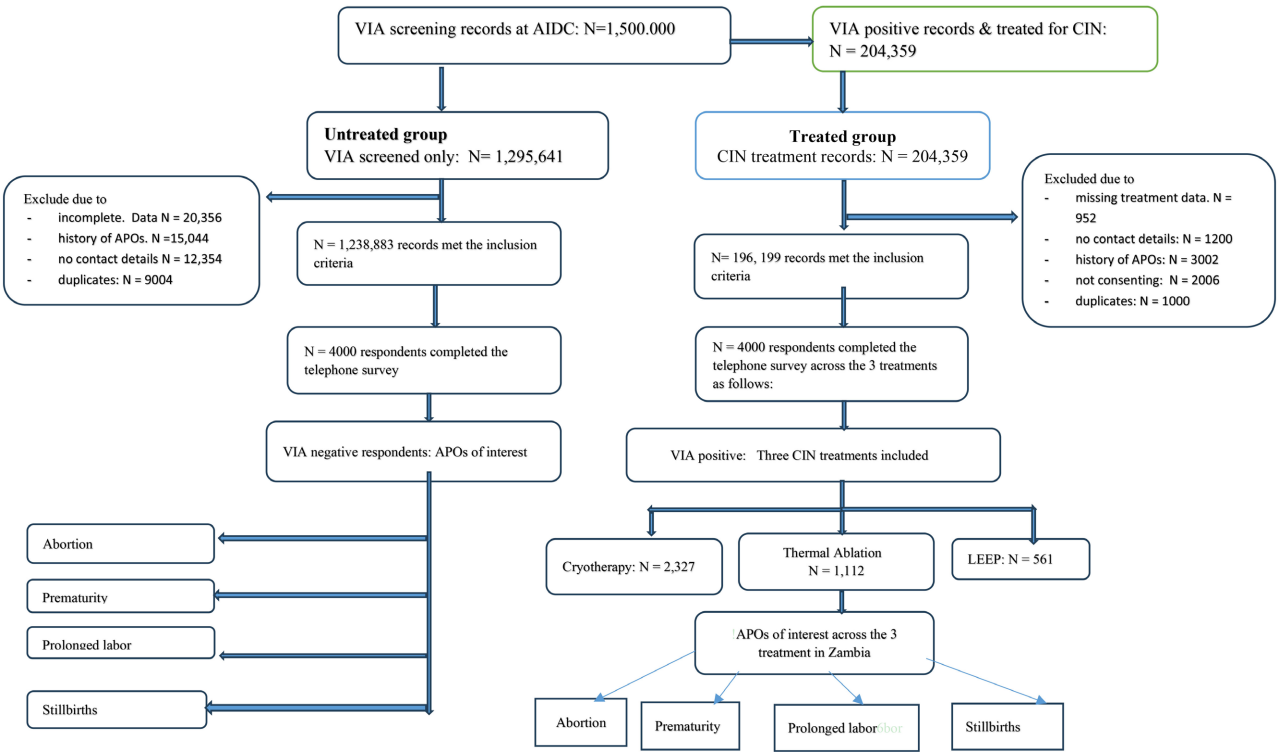

Figure 1. Study population and outcomes of interest flow chart.

The sample size for both groups was determined using the sample size calculation to compare two proportions [14]. The calculation adopted an 18.5% prevalence from a pilot study in Zambia [13]. The calculation further assumed 90% power, 95% confidence level, and a 5% minimum clinically significant difference in adverse outcomes between groups. Census sampling was used to sample the records. The data was directly entered into Stata version 16 on a password-protected laptop. To protect privacy, personal identifiers like respondents' names were omitted from the data set and replaced with a research number. The information was confirmed, cleaned, and exported to Stata version 16 for statistical analysis. Descriptive statistics determined the prevalence of APOs and obtained the frequency distribution in the study population. Chi-square and Fisher's exact test established the associations at 95% CI. All tests were conducted at a 5% significance level, and confidence intervals were set at 95%. Univariate and multivariable

binary logistic regression estimated the odds of adverse pregnancy outcomes across the three treatments. Potential confounders of the association between CIN treatment and pregnancy outcomes were identified based on published literature and clinical experience and included age, parity, education, smoking, HIV status, gestation age, mode of delivery, screening/ treatment interval and economic status.

The different study groups in the flow charts were the VIA-screened and CIN-treated groups, with treatment used for the treated group and outcome of interest for both groups.

3. Results

Socio Demographic Data

The socio-demographic characteristics of the respondents are shown in Table 1.

Table 1 shows that most were aged 31 - 40 years (60%; n = 8000) and 20 - 30 years (22.9%; n = 8000), and the majority were in the same age groups (20 - 30 and 31-40) at delivery. About, (48.1%) of the respondents attained secondary-level education, and 47.9% and 26.1 % were in the upper and lower middle economic class, respectively (Table 1).

Table 1. Socio-demographic characteristics of the respondents (n = 8000).

Characteristic	Levels	Treatment group		Total n (%)
		Treated = 4000 n (%)	Untreated = 4000 n (%)	
Age	<20 years	574 (14.4)	39 (0.97)	613 (7.7)
	20 - 30 years	789 (19.7)	1044 (26.1)	1833 (22.9)
	31 - 40 years	2029 (50.7)	2775 (69.4)	4804 (60.0)
	41 - 50 years	608 (15.2)	142 (3.6)	750 (9.4)
Age at delivery	<20 years	187 (4.7)	50 (1.3)	237 (3.0)
	20 - 30 years	1500 (37.5)	1548 (37.8)	3048 (38.1)
	31 - 40 years	2165 (54.1)	2299 (57.5)	4464 (55.8)
	41 - 50 years	148 (3.7)	103 (2.6)	251 (3.1)
Level of education	Primary	1394 (34.9)	319 (8.0)	1713 (21.4)
	Secondary	1021 (25.5)	1422 (35.6)	2443 (30.5)
	Tertiary	1585 (39.6)	2259 (56.5)	3844 (48.1)
Socio-economic status	Upper middle	1717 (42.9)	2118 (52.9)	3835 (47.9)
	Lower middle	891 (22.3)	1198 (30.0)	2089 (26.1)
	Other	1392 (34.8)	684 (17.1)	2076 (26.0)

Figure 2 shows that normal outcomes were more in the untreated groups (57.7% vs 42.3%) than in the treated. Furthermore, the treated group accounted

for the majority of abortions, 782 (74.5%), and prolonged labor, 659 (72.5%), whereas the untreated group accounted for higher proportions of prematurity, 122 (53%) and stillbirths, 36 (66.7%).

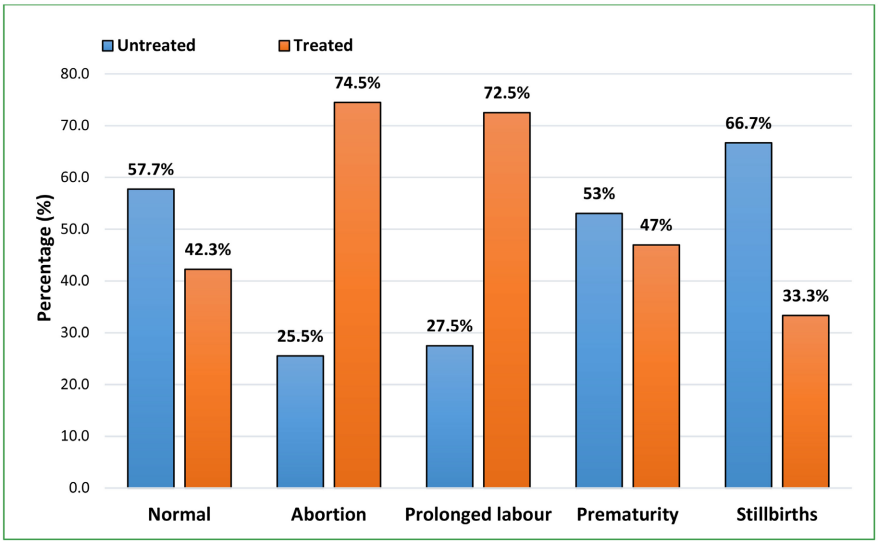

Figure 2. Adverse pregnancy outcomes among the respondents (n = 8000).

The prevalence and comparisons of pregnancy outcomes across the levels of treatment and among the outcomes of interest among respondents are shown in Table 2.

Table 2. Prevalence and comparison of pregnancy outcomes across levels of treatment and among the outcomes of interest (n = 8000).

Outcomes	Overall treatment		Treatment received			p-value
	Yes = 4000 n (%)	No = 4000 n (%)	Cryotherapy n = 4000 (%)	Thermal ablation N = 4000 (%)	LEEP N = 4000 (%)	
Adverse outcomes						
No	2433 (60.8)	3324(83.1)	1952 (83.9)	200 (18.0)	281 (50.1)	
Yes	1567 (39.2)	676 (16.9)	375 (16.1)	912 (82.0)	280 (49.9)	**<0.0001[C]**
Total	**4000 (100)**	**4000 (100)**	**2327 (58)**	**1112 (28)**	**561 (14)**	
Specific adverse outcomes						
Abortion	782 (49.9)	268 (39.6)	187 (49.9)	531 (58.2)	64 (22.9)	
Prolonged labour	659 (42.1)	250 (37.0)	124 (33.1)	357 (39.1)	178 (63.6)	**<0.0001[F]**
Prematurity	108 (6.9)	122 (18.1)	49 (13.1)	23 (2.5)	36 (12.9)	
Stillbirth	18 (1.1)	36 (5.3)	15 (4.0)	1 (0.1)	2 (0.7)	

LEEP = Loop Electrosurgical Excision Procedure, [C] = Chi-square Test, [F] = Fisher's Exact Test.

Table 2 shows that the APOs were more common among the respondents in the treated group (39.2%; n = 4000). APOs were more common among the clients who got thermal ablation (82%; n = 912), and cryotherapy was the most common treatment received (58%; n = 4000). When comparing outcomes between the

treated and untreated respondents, Abortions (49.9%; n = 1050) and prolonged labor (42.1%; n = 909) were high among the treated respondents, while stillbirths (5.3%; n = 54) and LBW (18.1%; n = 230) were more common among the untreated respondents. Thermal ablation accounted for the majority of APOs. There was a significant difference in the overall proportions of adverse outcomes across overall and specific levels of treatment ($p < 0.0001$). Similarly, the proportions of specific adverse pregnancy outcomes significantly differed across overall and specific treatment levels ($p < 0.0001$).

Table 3 shows results from unadjusted and adjusted logistic regression analysis. At both unadjusted and adjusted analyses, women treated with thermal ablation, or LEEP, had significantly increased odds of APOs compared to those without treatment. Results show that controlling for other variables in the model, women treated with thermal ablation (aOR = 5.05, 95% CI = 4.01, 6.36, $p < 0.0001$) and LEEP (aOR = 2.73, 95% CI = 2.20, 3.40, $p < 0.0001$) had five and two-times higher odds of adverse pregnancy outcomes respectively. Although treatment with cryotherapy showed reduced odds of adverse pregnancy outcomes, the effect was not statistically significant (aOR = 0.90, 95% CI = 0.75, 1.28, $p = 0.589$).

Table 3. Univariate and multivariable binary logistic regression analysis on the effects of treatment across the three treatments on APOs.

Variable	Unadjusted estimates			Adjusted estimates		
	cOR	95% CI	p-value	aOR	95% CI	p-value
Treatment						
None	Ref			Ref		
Cryotherapy	0.94	0.82 - 1.08	0.419	0.90	0.75-1.28	0.589
Thermal ablation	22.4	18.8 - 26.7	**<0.0001**	5.05	4.01-6.36	**<0.0001**
LEEP	4.90	4.07 - 5.89	**<0.0001**	2.73	2.20-3.40	**<0.0001**

cOR = Crude Odds Ratio, **aOR** = adjusted Odds Ratio, **CI** = Confidence Interv.

4. Discussion

The study demonstrated that comparing CIN treated and untreated women showed a difference in APO prevalence (39.2% vs.16.9) across the three treatments. Normal pregnancy outcomes were lower in the treated (42.3%; n = 4000) than in the untreated (57.7%; n = 4000). LEEP and thermal ablation treatments were associated with increased odds of APOs. Our study further showed that CIN treatment is linked to higher chances of experiencing abortion and enduring prolonged labor.

Most participants were between 31 - 40 years old (60%) and 20 - 30 years old (22.9%), with these same age ranges (20 - 30 at 38% and 31 - 40 at 55.8%) observed at the time of delivery. This aligns with prior findings that these ages represent peak reproductive years, during which most women receive antenatal information, facilitating informed choices about cervical cancer screening [15]. Most

respondents with tertiary education utilized the screening and treatment services more than those with lower attainment. This result might be because formal education provides better opportunities for women to comprehend the science during cervical cancer elimination campaigns. This finding is consistent with [16], who found that having a lower educational status was accompanied by low maternal and neonatal service utilization.

In this study, most of the respondents belonged to the upper 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. This finding corroborates that of [17], who reported that women in low social classes tend to have lower screening participation rates than those in higher classes. The primary structural hurdles were the geographical distance to screening facilities, accompanying travel expenses, inadequate transportation, and screening costs [18]. Travel expenses were a barrier in Africa, Asia, and South America, whereas screening fees were a barrier on all continents [19]. The prevalence of APOs among the treated and untreated reproductive-age women in Zambia was 39.2% vs.16.9%. This prevalence is slightly higher than that of a study conducted in Sweden (32% vs. 13%) [20] and a pilot study conducted in Zambia (18.5% vs. 5.4%). This might be due to the difference in demographic characteristics of the respondents, sample size, and the type of CIN treatment that was utilized. However, a number of factors may contribute to this variation in the risk for patients who have undergone these procedures [21].

Normal outcomes were lower in the treated group (42.3%) compared to the untreated group (57.7%). This could be because the untreated group did not experience any cervical discomfort before their pregnancy. Abortion (74.5% vs 42.3%) and prolonged labor (72.5% vs 25.5%) were the frequently recorded outcomes in the treatment group, while preterm births (53% vs 47%) and stillbirths (66.7% vs 33.3) were more common in the untreated group; this finding has not been previously reported (**Figure 2**). Similarly, across the three treatments, Abortion (49.9% vs 39.9%) and prolonged labor (42.1% vs 37%) were higher in the treated group compared to the untreated. Prematurity (6.6% vs 18.1%) and fresh stillbirths (1.1% vs 5.3%) were frequently recorded among the untreated group. The observation of higher APOs in the treated group aligns with a previous pilot prior to this study, which found that APOs are common among women who have undergone CIN treatment. However, the difference between this study and the pilot study is that stillbirths were the only APO more prevalent among untreated women [13]. Other previous studies further reported that CIN treatment was associated with a further increased risk of APOs and recommended that pregnancies after CIN treatment should be regarded as high-risk pregnancies and that women should be counseled accordingly [22] [23]. Our results contradict those of [24] [25], that concluded that CIN treatment increases pregnancy rate and is not associated with obstetric complications.

We noted varying results among the three treatments used in the country for

managing CIN. Cryotherapy and thermal ablation are considered ablative therapies, whereas LEEP is an excisional therapy. Cryotherapy utilizes extremely cold substances, such as nitrogen or argon, to freeze and eliminate abnormal cells on the cervix. In contrast, thermal ablation works by heating the Transformation Zone (TZ) epithelium to around 100°C. Although both therapies have similar effectiveness, thermal ablation offers a quicker alternative to cryotherapy and does not require a gas supply [26]. The loop electrosurgical excision procedure (LEEP) involves using a thin wire loop to remove precancerous or cancerous cells. LEEP has side effects of cervical stenosis and premature labor if a woman decides to get pregnant in the future [27]. 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. It was not associated with increased odds of APOs after treatment, though the effect was not statistically significant (aOR = 0.90, 95% CI = 0.75 - 1.28, p = 0.589). This could be because cryotherapy may not damage the cervical fibrous ring structurally and instead employs extremely low temperatures to kill the dysplastic cells. This finding has important implications for the management of women with CIN. This implies that cryotherapy should be the preferred treatment method for women of reproductive age when there are no contraindications to its use. This study's finding corroborates with that of [28], who demonstrated that cryotherapy was not associated with an increased risk of APOs. However, our finding is inconsistent with a systematic review that revealed that all forms of local cervical therapy techniques, whether destructive or excisional, are linked to a higher risk of preterm birth and unfavorable obstetric sequelae [10].

Women treated with Thermal ablative treatment had five times higher odds of APOs (aOR = 5.05, 95% CI = 4.01 - 6.36, p < 0.0001). These findings indicate that the choice of treatment modality for CIN may have implications for subsequent pregnancies and should be carefully considered. Caution should be exercised while performing excisional therapy on women who are of reproductive age. This finding is consistent with that of [29] which showed that ablative treatment was associated with pregnancy loss. The increase in odds has also been echoed in other studies by [21] [30], which revealed thermal ablation had higher rates of adverse outcomes even after adjusting for confounders [31]. Our finding that thermal ablative treatment is linked to a higher risk of pregnancy loss contradicts the results of previous studies on this association (RR = 0.65, 95% CI = 0.39 - 1.09) and needs to be verified by further research [28] [29]. The high reported positive association between APOs and thermal ablation treatment has not been previously reported and requires further investigation.

Receiving LEEP treatment increased the odds of APOs by two-fold (aOR = 2.73, 95% CI = 2.20 - 3.40, p < 0.0001). This means that women who conceive after LEEP have an almost twofold higher risk of APOs. LEEP excises the cervical tissue and may cause a structural severance of the cervical fibrous ring. This may diminish the cervix's supportive capacity as pregnancy advances. This could be one of

the explanations for the increased risk of abortion and prolonged labor by LEEP, which was not observed for cryotherapy treatment. This result is similar to that of [23] [28] [31] [32] that suggested that all excisional treatments are associated with the risk of APOs, including prematurity and miscarriage. Additionally, a pilot study prior to this study that reported that CIN treatments, particularly LEEP, are associated with significantly increased odds of adverse pregnancy outcomes supports this finding [13]. Furthermore, [32] showed that LEEP is associated with an increased risk of premature birth. Thus, LEEP must only be carried out on a genuine indication; otherwise, it will become a victim of its success. This finding of LEEP having a high risk for APOs implies that it is still essential to find a safer and more effective treatment for young women with CIN, and physicians should pay attention to the risk of APOs after LEEP. Our study did not find evidence that CIN treatment affects stillbirth and prematurity after treatment, making our finding differ from that of [33], which found that CIN treatment does affect prematurity or miscarriage (9.89% vs. 14.2%) in the untreated group.

5. Conclusion

Cervical treatments among Zambian women increase the risk of abortion and prolonged labor. These findings are significant for the management of women with cervical CIN. Cryotherapy should be prioritized for women of reproductive age, while thermal ablation and LEEP require careful consideration due to their association with increased risks of APOs. Therefore, caution should be taken when administered to those who are of reproductive age, and vigilant monitoring should be maintained during pregnancy, delivery, and the postpartum period to improve maternal and neonatal health. Women should be informed about their future risk of adverse pregnancy outcomes, particularly abortion and prolonged labor after thermal ablation and LEEP treatments for cervical lesions. Further research is needed to confirm these findings and explore safer treatment options for reproductive age women.

Limitations of the Study

This study was not without limitations. Even though we had access to the records for the majority of treated women, some women's records were incomplete, and the thickness of the excisional surgery was not consistently documented. We had no information on cone depth, limiting our ability to study the effect of thick excisional cervical surgical procedures on the specific outcomes of interest. This made it impossible to determine which cone size or volume was removed. The respondents with no phones or changed phone numbers did not participate in the study.

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Conflicts of Interest

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

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