

Pregnancy and Obstetrical Outcomes Following Treatment for Cervical Intra-Epithelial Neoplasia (CIN) in Two Hospitals of a Low-Resource Country

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Abstract

Objective: In Cameroon, more than 80% of women suffering from cervical intraepithelial neoplasia (CIN) are within the reproductive age. This study intended to analyze the pregnancy outcomes following cervical treatment in Cameroon. **Methods:** This was a cohort study with two years retrospective data collection involving 82 women who underwent cervical treatment for CIN in two Cameroonian hospitals from January 2015 to December 2017. Data were collected from CIN treatment to end of pregnancy where applicable. Data analysis was done using Epi Info software version 3.5.4. **Results:** We collected data from 82 patients aged 27 to 48 years, with a mean age of 36.5 (SD: 5.3) years. During the study period, 33 out of 82 participants became pregnant 40.2 [29.56 - 51.66]%. The factor associated with pregnancy occurrence after treatment was age less than 35 years (Odds ratio = 4.37 [1.7 - 11.2]). From the 33 pregnancies recorded, 17 (51.5%) ended in a delivery, amongst which 15 (88.2%) were vaginal. **Conclusion:** Pregnancy frequency over two years following cervical treatment for CIN was relatively good, and younger women (age < 35 years) were significantly more like to have conceived compared to their older counterparts. Post-treatment delivery outcomes seem to be similar

to those in the general population.

Keywords

Cervical Intraepithelial Neoplasia, Cervical Treatment, Pregnancy Outcome

1. Introduction

Cervical intraepithelial neoplasia (CIN) is defined as precancerous lesions caused by HPV (human papilloma virus), comprising three stages: CIN 1, CIN 2, and CIN 3 [1]. The World Health Organization (WHO) recommends that high-grade CIN be treated by fertility-preserving methods which include ablativ treatments (cryotherapy and thermalablation) or excisional methods (large loop excision of the transformation zone (LLETZ), large electrosurgical excision procedure (LEEP) and cold knife conisation) [2] [3]. Thermalablation equipment is simple, easily portable (less than 2 kg), and is among the methods of choice used for the treatment as recommended by WHO [3] [4] [5]. In Cameroon, the treatment methods used are cryotherapy, thermalablation, and conisation.

Studies in America and Europe on pregnancy after CIN cervical conisation reported obstetrical complications including premature rupture of membranes, premature delivery, low birth weight, associated with increased perinatal mortality [6] [7]. Evidence on the impact of thermal ablation and cryotherapy on fertility and premature delivery is still uncertain.

In 2013, a Cameroonian study reported a cervical dysplasia percentage of 3.9%, and the age group of 34 to 49 years to be the most affected [8]. In 2017, another study in the same country registered 14% of high-grade intraepithelial lesions in women aged 30 to 49 years, a majority of which still had future pregnancy desires [4]. Little is known about pregnancy rate and their outcome after fertility-preserving treatment methods for CIN in Cameroon.

The objective of the study was to assess the pregnancy rate and obstetrical outcome after locally cervical treatment of CIN in Cameroon.

2. Materials and Methods

2.1. Study Design, Setting and Period

This was a cohort retrospective study involving patient's record review with associated patient interview conducted in the Departments of Gynaecology and Obstetrics of two Cameroonian hospitals; the Yaoundé University Teaching Hospital (YUTH), and the Dschang District Hospital (DDH). The YUTH is a central level health facility located in urban Cameroon (Yaoundé, the political capital of Cameroon) while the DDH is a first level referral hospital in the health pyramid, located in a semi-rural area. Each of these hospitals offers preventive and curative care for precancerous lesions of the cervix to more than 1 000

women per year. The study period spanned from January 2015 to December 2017 and the data was collected in March 2018.

2.2. Study Population

We included all women aged 25 - 49 who underwent locally cervical treatment for CIN in the two settings and who expressed a desire for pregnancy in the future. We excluded women who did not come for the interview, those not exposed to pregnancy (not sexually active since treatment or on contraception or who declared at interview that they avoided pregnancy during the study period), and those with incomplete medical records. Also, all women with a post-therapeutic experience of less than two years were not included. Of the 252 women treated for CIN, 126 expressed a desire for pregnancy, out of which 82 were eligible.

Our sample size was exhaustive, enrolling all women who met our inclusion criteria.

2.3. Procedure of Implementation and Data Collection

Administrative authorizations were obtained from the directors of both settings. Data collection was done by a review of patients' records and face to face through an interview by a medical student trained on the consenting and data collection procedure. The data collection tool was a questionnaire, which was composed of questions on the women's socio-demographic characteristics, past fertility/obstetric history, cervical treatment administered, and questions to evaluate their post-therapeutic exposure to sexual intercourse as well as their pregnancy status and outcomes following treatment. Medical records of women treated by local cervical methods for precancerous lesions were reviewed to collect preliminary existing information on the predesigned data collection sheet. Women were called by phone or approached during their normal scheduled consultations for this procedure. After a complete explanation of the information sheet of the study to the woman consent to participate was obtained, concretized by the signing of the informed consent form. The questionnaire was administered face-to-face and one-to-one in closed settings.

2.4. Data Analysis

The statistical software Epi-Info version 3.5.4 was used for data analysis. Proportions with their 95% confidence intervals were calculated for categorical variables. Means or medians (where applicable) were calculated for continuous variables. The homogeneity of the distribution of variables around pregnancy occurrence and non-pregnancy occurrence groups was assessed using Pearson Chi square test or Fisher exact test. Associations were quantified using Crude Odd Ratio (OR) and their 95% confidence intervals, and when appropriate, adjusted Odd Ratio Ratio (OR^a) by multivariate analysis. The level of significance was set at $p < 0.05$.

2.5. Ethical Considerations

Ethical approval was obtained from the institutional ethical review board of the

“Université des Montagnes” (N°2018/066/UdM/PR/CIE). Participants were included after a written informed consent, the data collection tool was anonymous and information collected kept confidential.

3. Results

3.1. Pregnancy Occurrence

During the study period, 252 women were treated for CIN, and among them 126 expressed pregnancy desires. Pregnancy occurred in 33 of 82 women (40.2%). Participant’s ages ranged from 27 to 48 years, with a mean age of 36.5 ± 5.3 years. **Table 1** presents the baseline clinical characteristics of the participants stratified by pregnancy occurrence.

The pregnancy rate among women aged less than 35 years was 60.0% as opposed to the 25.5% registered in older women, the difference being statistically significant ($P = 0.001$). Pregnancy rate was significantly higher in participants with past history of contraception (64.3%) than in those who have never used it (35.3%). Past history of sexually transmitted infection and of infertility were not associated with higher rate of post-therapeutic pregnancy. Factors associated with pregnancy occurrence after treatment, are presented in **Table 2**.

Age below 35 years crude odd ratio (OR^a) = 4.37 [1.7 - 11.22] and history of

Table 1. Baseline clinical characteristics of the participants stratified by pregnancy occurrence.

Characteristics	Total (N = 82)	Pregnancy after treatment				p-value
		Yes		No		
		N = 33	%	N = 49	%	
Mean age (SD ^a)	36.5 (5.3)	34.5 (4.7)		37.8 (5.3)		0.0067
Age group						0.001
<35	35	21	60.00	14	40.00	
≥35	47	12	25.5	35	74.5	
Past history of contraception						0.043
Yes	14	9	64.3	5	35.7	
No	68	24	35.3	44	64.7	
Past history of STI						0.379
Yes	19	6	31.6	13	68.4	
No	63	27	42.9	36	57.1	
Past history of infertility						0.143
Yes	7	1	14.3	6	85.7	
No	75	32	42.7	43	57.3	

^aStandard deviation.

Table 2. Factors associated with pregnancy occurrence following cervical treatment for CIN (bivariate and multivariate analysis).

Characteristics	Pregnancy after treatment				OR ^a (IC95%)	p	^b OR	p	
	Total (n = 82)	Yes (n = 33)		No (n = 49)					
		n	%	n					%
Age less than 35									
Yes	35	21	60.0	14	40.0	4.37 (1.7 - 11.2)	0.001	3.66 (1.3 - 10.32)	0.014
No	47	12	25.5	35	74.5	1 ^c		1 ^c	
Contraception									
Yes	14	9	64.3	5	35.7	3.3 (1.03 - 10.9)	0.043	2.67 (0.65 - 11.26)	0.179
No	68	24	35.3	44	64.7	1 ^c		1 ^c	
Past history STI									
No	63	27	42.9	36	57.1	1.62 (0.54 - 4.82)	0.379	4.73 (0.44 - 49.94)	0.196
Yes	19	6	31.6	13	68.4	1 ^c		1 ^c	
History of infertility									
No	75	32	42.7	43	57.3	4.46 (0.51 - 38.94)	0.143	1.35 (0.39 - 4.71)	0.630
Yes	7	1	14.3	6	85.7	1 ^c		1 ^c	

OR^a crude Odds Ratio; OR^b adjusted Odds Ratio; ^cReference; P: P-value.

contraceptive use: OR^a = 3.3 [1.03 - 10.9] were associated with increased likelihood of pregnancy occurrence. During multivariate analysis, only the age below 35 years was associated with the occurrence of pregnancy following cervical treatment of CIN adjusted odd ratio (OR^b) = 3.66 [1.3 - 10.32].

3.2. Pregnancy Outcomes

The flow chart (**Figure 1**) presents pregnancy outcomes within the study population.

Among the 82 treated women who expressed fertility desires, thirty-three pregnancies were recorded 40.2%, out of which 13 (51.5%) ended in childbirth and 6 (18.2%) were still in progress at the end of the study. There were 5/33 (15.2%) spontaneous abortions, 2 in the first trimester, and 3 in the second trimester. There were also 5/33 (15.2%) induced abortions, initiated by women who estimated the occurrence of their pregnancies to be too early.

Finally, 17 women gave birth among which, 15 normal term vaginal deliveries (88.2%), one term cesarean section (5.9%), and one preterm vaginal delivery (5.9%). A single second-trimester abortion was recorded among participants from each treatment entity, (*i.e.*: conization, cryotherapy, and thermal ablation).

Pregnancy occurrence over time from treatment is shown in **Figure 2**.

Pregnancies were mostly recorded between the 10th and 12th-month post-therapy.

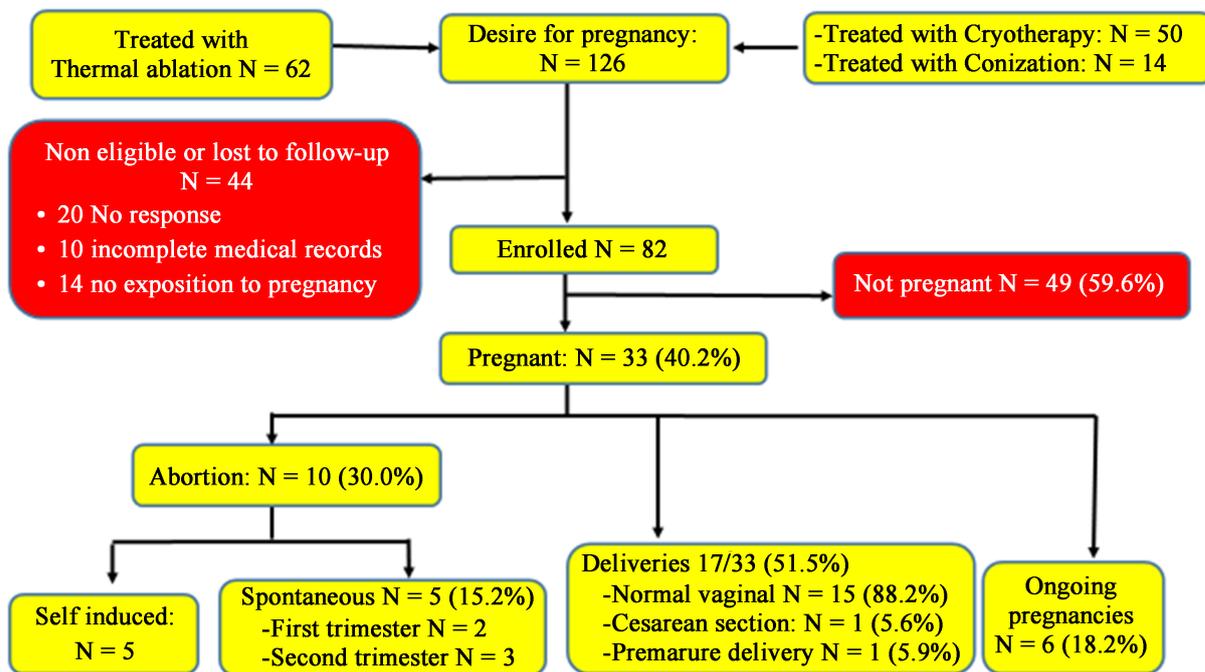


Figure 1. Flow diagram of study population.

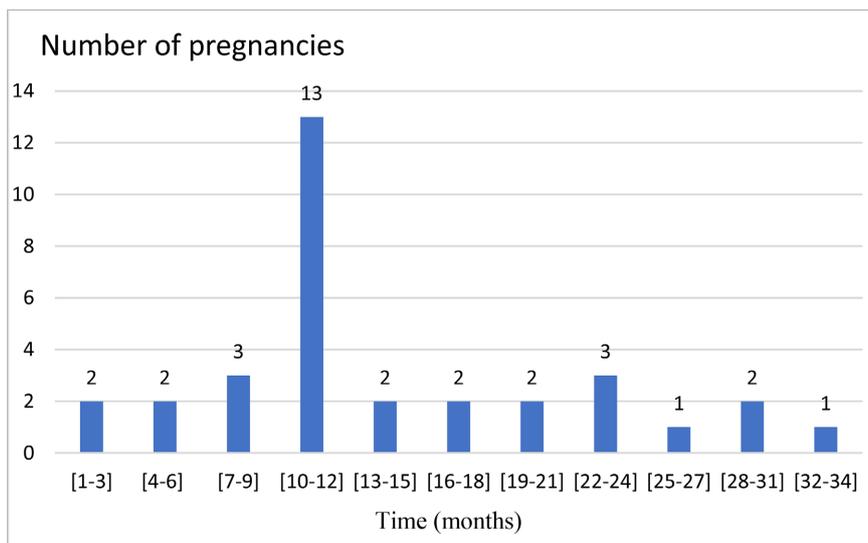


Figure 2. Number of pregnancies over time (in months) from treatment

4. Discussion

The study aimed to determine the pregnancy occurrence and outcome in women after cervical treatment for CIN. This pilot study is the first step to provide an answer to one of the main worries about cervical cancer prevention, which is childbearing after treatment. As an addition to other studies, all our participants had biopsy-proven CIN.

We found a post-therapeutic pregnancy rate of 40.2%, similar to the 43% reported by Kyrgiou in a meta-analysis of four studies including 38,050 participants [6]. This percentage is higher than the 20% rate reported in France by

Omnès *et al.* on 20 patients all treated by conisation in 2003, and the 12.78% obtained by Chafika *et al.* in 2004 on a larger size of 460 patients all treated by conisation in France [9] [10]. Our pregnancy rate is also higher than the 14% found by Naleway *et al.* in a meta-analysis including 4127 patients treated with different fertility-preserving methods (Cryotherapy Large Loop Excision of Transformation Zone and Cold knife biopsy), apart from thermal ablation [7]. This can be explained by the fact that their most representative age group was 20 to 29 years, ages at which the majority of women in the developed countries where these studies were carried out do not yet express the desire for maternity [7] [9]. Another possible explanation is that more than half of their patients were on contraceptives during the study period [9]. Our reported post-therapeutic pregnancy rate is however low compared to the normal cumulative conception rates described in the general population. Cumulative spontaneous conception rates stand at 75% after 6 months, 90% after a year, and 95% over two years [11]. This rate is described to drop significantly in the 30 s and 40 s (typical of our study population given that the mean age of our participants was 36.5 ± 5.32) to about 60% over a year and 85% in two years among women aged 35 - 39 years [11].

History of contraceptive use before treatment also appears to be a factor increasing by 3 folds the chances of having a pregnancy, (crude OR 3.3 [1.03 - 10.9]), p-value: 0.04. This can be explained by the fact that only potentially fertile women generally seek contraception. After screening and treatment, most of them stop using contraception to fulfill their childbearing desire before any possible pathology that may compromise their fertility.

Age below 35 years appears to be significantly associated with higher post-therapeutic pregnancy rate (crude OR: 4.37 [1.7 - 11.2], p = 0.001). This is the only significant factor increasing the chances of having a pregnancy by more than four-folds. In rural areas of low-resource countries, a majority of women have already attained their desired number of children by the age of 35. Those with pregnancy desires beyond that age may be hypo or infertile. According to the Demographic and Health Survey 5 of Cameroon, the fertility rate by age group falls from 196/1000 to 139/1000 between the 30 - 34 and 35 - 39 years age groups respectively [12]. However, given that our sample size was small, large scale studies are still needed to be able to fully identify factors associated with pregnancy following cervical treatment of CIN.

As concerns pregnancy outcomes, of the 33 pregnancies, 17 (51.5%) ended in childbirth. Among the 17 deliveries, we noted 15 (88.2%) term vaginal deliveries. Our observed 5.9% cesarean section rate falls within the range of 5% to 15% recommended by the WHO [13].

We recorded 5.9% (1/17) premature delivery, a percentage lower than 7 to 14% reported by Kirgiou *et al.* in 2006 in a systematic review, the percentage being higher in women treated with conization [14]. Our recorded percentage ranges within the WHO estimated 5% - 15% in the general population [15]. However, our results are questionable due to the small sample size. Nonetheless, this observation allows us to support that fertility-preserving treatments may not

be a risk factor of premature deliveries while waiting for the results of studies with larger sample sizes.

We found five cases (15.2%) of participant-initiated induced abortions, all in women who conceived within the first nine months following treatment because they considered their pregnancy occurred too early. The WHO recommends a 12 months follow-up after cervical fertility-preserving treatment of CIN [2]. Consequently, the early conception and subsequent participant-initiated induced abortions observed in our study stress the need for a one-year contraception prescription following local cervical treatment of CIN.

A spontaneous abortion rate of 15.2% was observed, with a predominance of late abortions (3/5). A Norwegian study reported that the miscarriage rate increases with women's age, from 10% at the age of 30 to 30% at the age of 40 [16]. With the 15.2% pregnancy loss found in our study, we can conclude that fertility-preserving cervical treatment for CIN may not increase the risk of pregnancy loss.

The study gives some pilot information on pregnancy outcome after cervical treatment of CIN. The limits are mainly those related to the retrospective data collection, the small sample size, and the lack of control.

5. Conclusion

The two years cumulative pregnancy rate following cervical fertility-preserving treatment of CIN is 40.2%, with age below 35 years associated with a higher pregnancy occurrence. Post-treatment delivery outcomes seem to be similar to those in the general population. These results need to be confirmed by studies with larger sample sizes. There is a high rate of women-initiated induced abortion for those that conceived within the first months after treatment, stressing the need of inserting a contraceptive package in cervical cancer prevention activities.

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Conflicts of Interest

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

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