



Full length article

Obstetric outcomes in patients who have undergone excisional treatment for high-grade cervical squamous intra-epithelial neoplasia



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ABSTRACT

Objective: To evaluate the relationships between excisional treatment for high-grade cervical intra-epithelial neoplasia (CIN2+) and obstetric outcomes in terms of preterm delivery risk, premature rupture of membrane (PROM) and type of delivery, and between pre-term delivery and the type of excisional technique (radio frequency excision, laser conization).

Methods: This was a retrospective study of the obstetric outcomes of 2316 women aged 25–45 years who underwent excisional treatment for CIN2+ at the Obstetric and Gynecological Clinic of Ospedale Maggiore della Carità in Novara and at the Obstetric and Gynecological Department of Ospedale Sant'Anna in Torino in the period 2005–2014 and were evaluated until April 2016, and 57,937 untreated women of the same age, from the same centers.

Results: After treatment, 320 women had at least one pregnancy leading to delivery after a mean of 3.35 years. Treatment significantly increased the risk of preterm delivery. Compared with no treatment, the risk of preterm birth was higher in women who had undergone treatment (33.13% vs. 6.60%). Techniques removing or ablating more tissue, such as large loop excision of the transformation zone, were associated with worse outcomes (OR 2.96, 95% IC 1.72–5.10).

Smoking habits significantly increase the risk of preterm delivery in the treated women (OR 2.82, 95% IC 1.61–4.9).

The risk of premature rupture of the membranes (PROM) (40% vs. 23.22%), the risk of preterm PROM (pPROM) (13.13% vs. 2.71%) and dystocic births (18.75% vs 4.48%) were also significantly increased after treatment.

Caesarean sections were less frequent among the treated women (15.94% vs. 32.41%).

Conclusions: Our findings reveal a relationship between cervical excisional treatment and pre-term delivery, PROM, and the method of delivery. In order to minimise risk and guarantee the best obstetric outcome, patient treatment and follow-up should be personalised.

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Introduction

Cervical cancer is one of major concerns of women's health with about 530,000 new cases every year and 275,000 deaths. In Italy, it is the fifth most frequent after breast cancer, colorectal cancer, lung cancer and endometrial cancer, with an annual incidence of 3700 cases and 1550 deaths. This means that it affects seven out of 100,000 women/year, a reduction from the peak incidence of 30/100,000/year observed in the 1960s and 1970s [1].

Invasive tumours are preceded by high-grade cervical intra-epithelial neoplasia (CIN2+), although only 12.30% subsequently

develop carcinoma, the incidence of which is 35/100,000 Italian women.

The international guidelines indicate that the excision procedure is the CIN treatment of choice [2,3], which has become anatomically more conservative and more personalised over the last ten years. The aim of the treatment is to remove pre-cancerous lesions while preserving cervical anatomy [4]; however, as most of the women affected have not completed their reproductive cycle and the treatment may give rise to obstetric complications such as premature births, the management of patients undergoing excisional treatment remains a controversial subject of debate. It is not fully known why cervical excision can lead to negative obstetric outcomes, but it has been supposed that it may compromise the integrity of the cervical stroma and give rise to collagen alterations, immunological

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factors, or changes in the vaginal flora associated with human papillomavirus (HPV) infection.

The aim of this retrospective study of our patient database was to evaluate the risk of premature births, premature rupture of membrane (PROM), and preterm PROM (pPROM) and the type of delivery in women who have undergone excisional procedures for CIN2+.

Materials and methods

This retrospective observational study included 2316 women aged 25–45 years who had previously received local excisional treatment for CIN2+ between January 2005 and December 2014 at the Cervical-Vaginal Pathology and Laser Surgery Centre of the Obstetric and Gynecological Clinic of Ospedale Maggiore della Carità in Novara and at the Colposcopy and Laser Surgery Centre of the Obstetric and Gynecological Department of Ospedale Sant'Anna in Turin (both of which are reference centres for second-level cervical screening in Piedmont). Obstetric outcomes were evaluated until April 2016.

The inclusion criteria were:

- A Papanicolau test carried out by the Pathological Anatomy Services of Novara and Turin.
- A colposcopy examination, the results of which were described in accordance with the 2002 International Classification of Barcelona as revised by the 2011 International Classification of Rio.
- Family, personal and obstetric history (if unknown, the patient was contacted by telephone): age, parity, smoking habits, previous cervical treatment, parity after treatment, type of delivery, gestational age at the time of delivery, PROM and gestational age at the time of PROM.
- Single or multiple biopsy and/or endocervical curettage under colposcopic guidance with a histological diagnosis revised in accordance with the Lower Anogenital Squamous Terminology (LAST) Standardization Project for HPV-associated Lesions. Background and Consensus Recommendations from the College of American Pathologist (CAP) and the American Society for Colposcopy and Cervical Pathology (ASCCP).
- Excisional treatment according to the 2011 International Classification of Rio: type 1 (the transformation zone is completely exocervical and fully visible); type 2 (the transformation zone has a fully visible endocervical component); type 3 (the transformation zone has an endocervical component that is not fully visible). The techniques included laser conisation, RF excision of the transformation zone and large loop excision of the transformation zone, also known as loop electro-surgical excisional procedure.
- A histological examination of the excised sample, with a description of the base and height of the cone, the possible involvement of glandular crypts, margins (exocervical, endocervical, deep), considered positive when the lesion-margin distance was ≤ 1 mm. If the margins were not described or the sample was opened before measuring its height, the sample was classified as not assessable.
- The depth of laser vaporisation or RF treatment measured on the surgical bed using a ruler.
- Adherence to the follow-up protocol of the two colposcopic centres:
 - I Control colposcopy one month after treatment
 - II Pap test and colposcopy 4–6 months after treatment
 - III Pap test and colposcopy every six months for two consecutive years
 - IV Pap test and colposcopy every year for five consecutive years

V Annual Pap test after five years of negative follow-up

In the case of relapse or disease persistence, biopsy and/or curettage in order to continue the follow-up or re-conisation.

- The time between treatment and delivery: the follow-up of each patient was calculated from the day of treatment to the day of delivery, and had to be a minimum of two years. Follow-up was terminated in April 2016.

All of the patients underwent excisional treatment when histologically diagnosed as CIN2+ after one or more biopsies and/or endocervical curettage or in the case of a cyto-histological discrepancy.

The control group consisted of 57,937 patients who gave birth between 2005 and 2016 at the two participating hospitals with no history of treatment for CIN 2+. This data comes from a total of 97,072 births obtaining a population with a rapport case-control of 1:173.

The data collected from the hospital databases included parity, smoking habits, age at the time of delivery, gestational age, PROM, pPROM, gestational age at the time of PROM, type of delivery (eutocic, dystocic, Caesarean), and complications.

The exclusion criteria for the women underwent excision were:

- ○ ○ ○ A histological diagnosis of CIN1 or glandular dysplasia
 - No pregnancy after excisional treatment
 - Poor compliance or loss to follow-up
 - Cold Knife Conization

The exclusion criteria for both groups were:

- ○ ○ ○ Multiple pregnancies, a previous pre-term delivery, pathological pregnancy (intrauterine growth delay, pre-eclampsia, placenta praevia, gestational diabetes) and fetal pathologies.

Statistical analysis

The variables putatively associated with the Preterm Delivery were analysed by use of a univariable logistic regression model. The variables selected by the univariable analysis were entered into a multivariable logistic model using a forward stepwise elimination algorithm (terms with $P > 0.05$ were eligible for removal).

The differences between proportions were evaluated using normal approximation.

A P -value ≤ 0.05 was considered statistically significant.

Stata Statistical Software (release 13.0 College Station, Stata Corporation, TX, USA) was used in all the statistical analysis.

Results

2,316 women aged 25–45 years underwent excisional treatments for CIN2+ between 2005 and 2014, 320 of whom experienced a pregnancy ending with birth within 3.35 ± 2.18 years of treatment and before April 2016.

The risk of preterm delivery was higher among the treated women (33.13% vs 6.60%; $p < 0.0001$). Stratification of the preterm births by gestational age showed that the largest group of newborns (88.68%) had a gestational age of 34–36.6 weeks (late preterm delivery).

The main demographic characteristics of the populations are shown in Table 1 and in particular it should be noted that the risk of premature rupture of membrane (PROM) was increased after treatment (40% vs 23.22%), and cervical excision significantly affected also the risk of pPROM (< 37 weeks) ($p < 0.0001$).

Table 1
Main Characteristics of the 320 Treated Women and of the 57,937 Untreated Women.

Characteristic	Treated Women	Untreated Women	P
Years Between Treatment and Delivery, mean \pm SD, y	3.35 \pm 2.18		
Age at Treatment, mean \pm SD, y	31.65 \pm 4.49		
Age at Delivery, mean \pm SD, y	35.00 \pm 4.48	33.78 \pm 4.30	
Cone Depth, mean \pm SD, mm	14.48 \pm 6.61		
Smoker, n. (%)			
Yes	73 (22.81)		
No	247 (77.19)		
Nulliparous, n. (%)	216 (67.50)		
Multiparous, n. (%)	104 (32.50)		
Technique [†] , n. (%)			
RF 1	132 (41.25)		
RF 2/3	148 (46.25)		
Laser conization	40 (12.50)		
Term Delivery, n. (%)	214 (66.88)	54,118 (93.40)	
Preterm Delivery, n. (%)	106 (33.13)	3819 (6.60)	<0.0001
Very Low (<28 weeks), n. (%)	1 (0.94)	200 (0.35)	
Low (28 – <32 weeks), n. (%)	2 (1.89)	315 (0.54)	
Moderate (32 – <34 weeks), n. (%)	9 (8.49)	375 (0.65)	
Late (34 – <37 weeks), n. (%)	94 (88.68)	2929 (5.05)	
PROM, n. (%)			
Yes	128 (40)	13,452 (23.22)	<0.0001
No	192 (60)	44,485 (76.78)	
pPROM, n. (%)			
Yes	42 (13.13)	1572 (2.71)	<0.0001
No	278 (86.88)	56,365 (97.29)	
Type of Delivery, n. (%)			
Eutocic	209 (65.31)	36,562 (63.11)	0.415
Dystocic	60 (18.75)	2595 (4.48)	<0.0001
Caesarean Section	51 (15.94)	18,780 (32.41)	<0.0001

[†] RF 1: radio frequency excision of the transformation zone; RF2/3: large loop excision of the transformation zone.

Also the mode of delivery was affected by treatment; instrumental deliveries were not similar in the treated and untreated women (18.75% vs 4.48%, $p < 0.0001$) but the percentage of Caesarean sections was lower among the treated women (15.94% vs 32.41%; $p < 0.0001$).

In the univariable analysis the risk of preterm delivery among the treated women varied depending on their smoking habits, being significantly greater in smokers ($p < 0.0001$; OR 3.08, 95% CI 1.80–5.30). The type of treatment significantly affected the risk of preterm birth, that was significantly lower among the women undergoing type 1 RF excision than among those undergoing type 2/3 RF excision ($p < 0.0001$; OR 3.22, 95% CI 1.89–5.48); the difference in risk of preterm delivery between type 1 RF excision and laser conization was not significant ($p = 0.209$ OR 1.67, 95% CI 0.75–3.70) (Table 2).

The mean depth of excision was 14.48 \pm 6.61 mm. The univariate analysis suggested that the risk of preterm delivery increases with a cone depth > 14 mm ($p = 0.026$; OR 1.72, 95% IC 1.07–2.8) and the percentage of preterm deliveries increased by 0.3% for every mm of excised tissue ($p = 0.05$). (Table 2)

The percentage of post-treatment preterm deliveries was similar among nulliparous and multiparous women ($p = 0.535$; OR 0.85, 95% CI 0.52–1.40). There is no greater risk of preterm birth in women over forty years ($p = 0.7$; OR 1.10, 95% CI 0.69–1.76). (Table 2)

In the multivariable analysis smoking habits ($p < 0.0001$, OR 2.82, 95% CI 1.61–4.9) and type of treatment (type 2/3 RF, $p < 0.0001$, OR 2.96, 95% CI 1.72–5.10) remained significant whereas the depth of treatment was excluded. (Table 2)

Discussion

The management of women with CIN2+ is clinically important because many of them have not started or completed their reproductive cycle at the time of diagnosis and, in line with

Table 2
Univariable and Multivariable Analysis of Risk of Preterm Delivery.

	Preterm/Total (%)	OR (95% CI)	P
Univariable Analysis			
Age			
<40 years [*]	47/147 (32)		
\geq 40 years	59/173 (34.1)	1.10 (0.69–1.76)	0.7
Cone Depth			
<14 mm [*]	39/146 (26.7)		
>14 mm	67/174 (38.5)	1.72 (1.07–2.8)	0.026
Smoke			
No [*]	67/247 (27.1)		
Yes	39/73 (53.4)	3.08 (1.80–5.30)	<0.0001
Parity			
Nulliparous [*]	74/216 (34.2)		
Multiparous	32/104 (30.8)	0.85 (0.52–1.40)	0.535
Technique [†]			
RF 1 [*]	27/132 (20.4)		
RF 2/3	67/148 (45.3)	3.22 (1.89–5.48)	<0.0001
Laser conization	12/40 (30)	1.67 (0.75–3.70)	0.209
Multivariable Analysis			
Smoke		2.82 (1.61–4.9)	<0.0001
RF 2/3		2.96 (1.72–5.10)	<0.0001

Abbreviation: CI, confidence interval; OR, odds ratio.

^{*} Reference Group.

[†] RF1: radio frequency excision of the transformation zone; RF2/3: large loop excision of the transformation zone.

previously published data, our findings show that cervical treatment was associated with an increased risk of preterm birth and premature rupture of the membranes [5,6].

We found that the incidence of preterm deliveries was higher in treated than in untreated women (33.13% vs 6.60%) with 88.68% of late pre-term deliveries (\geq 34 weeks).

Our study also indicated smoking habits is a significant predictive risk factor of preterm delivery among the treated women, as evidenced in the univariate and multivariate analysis.

This result could be due to the smoking habits plays a role in persistence of HPV infection through the impairment of immune system [18]. Indeed there is agreement that treated women are more likely to experience a preterm delivery not only for the loss of cervical tissue and the mechanical support that it provides [15–17], but also for the changes in the immune system [18] and vaginal environment of women during pregnancy [20]. These changes play a very important role by promoting the persistence of HPV, thus favouring the development of frequent ascending infections and consequent prematurity.

Castanon et al. [7] found that the risk of preterm birth was 15.3% in women with large excision (especially over 15 mm) and 7.2% in those with a punch biopsy before birth compared with 6.7% in the general population in England, regardless of the time between treatment and conception.

The findings of previously published meta-analyses [8–14] are discordant, probably because the differences in the compared groups and the depth of excision associated with the treatment techniques, and the quality of the meta-analyses themselves.

There is agreement about the risk of premature births increased with the depth of the excision. The latest review by Kyrgiou et al. [19] reports a 1.54 risk of preterm delivery when the length of the cone is <10–12 mm, which increases to 4.91 when it is >20 mm. The findings of the 71 studies included in the meta-analysis of Kyrgiou et al. indicate that the risk is increased by both excisional and destructive procedures, but that women who undergo excisional procedures are more likely to experience obstetric sequelae. Our study also confirms that depth of treatment is a statistically significant risk factor of preterm birth only at univariate analysis. The risk was increased for excisions more than 14 mm in depth. It has previously been suggested that the impact of treatment on the risk of preterm birth might not be a consequence of treatment but rather a product of other confounders present in women with cervical disease [7,14,15].

However the multivariable analysis reported smoke and radical treatment techniques as the only predictive factors of preterm delivery. Specifically, the risk of preterm birth was higher for large loop excision of the transformation zone (type 2/3 RF), because deeper excisions significantly increased the risk of preterm births compared with less deep excisions. Probably the impact of treatment on the risk of preterm birth might be a consequence of the different depth reached by the different techniques.

We found that excisional treatment significantly increases PROM (40% vs 23.22%, $p < 0.0001$) and pPROM (13.13% vs 2.71% $p < 0.0001$), thus confirming that the removal of the transformation zone can destroy the cervical production of mucus [21]. However, the published data concerning the association between cervical excision and PROM are discordant.

Unlike most other studies [22], we found that Caesarean sections were less frequent among the treated women (15.94% vs 32.41% $p < 0.0001$).

The number of dystocic deliveries was statistically significant increased in treated women (18.75% vs 4.48% $p < 0.0001$).

Conclusions

Our data confirm that women who have undergone excisional treatment for CIN2+ have an increased risk of preterm delivery, PROM, pPROM and dystocic delivery and we confirm the

importance of smoke because it could change the vaginal environment influencing the viral load.

Treated patients should be informed about increased risk of preterm births and the obstetricians should offer the most appropriate treatment to optimize the chances of a healthy pregnancy without compromising the oncological outcome.

There is therefore a need for multicentre studies that would make it possible to extrapolate a “risk score” capable of providing women with personalised risk assessments and supporting physicians in offering adequate counselling concerning the potential obstetric sequelae of cervical excision.

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