Clinical Study

Risk of Preterm Delivery Associated with Prior Treatment of Cervical Precancerous Lesion according to the Depth of the Cone

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1. Introduction

Cervical intraepithelial neoplasia (CIN) is defined as a series of intraepithelial changes which includes nuclear pleomorphism, loss of polarity, and presence of abnormal mitoses. It is confined to squamous epithelium, but it may shift from a benign to a malignant lesion [1]. The risk of cervical cancer in women older than 30 years with carcinoma in situ is estimated at 31% [2].

Although the great majority of all HPV-infections resolve spontaneously within the first 2 years, the subset of infection remained has a high-persistence potential [3]. Management guidelines therefore recommend treatment for women with moderate-to-severe dysplasia [4, 5].

Surgical techniques currently adopted by the majority of the practitioners consist in ablative or excisional approaches. The excisional approach usually performed by laser conisation or large loop excision of the transformation zone (LLETZ) or cold knife conisation, offers advantages over the ablative method both permitting the histological investigation of removed lesion and ensuring a greater excision of cervical transformation zone. Indeed, incomplete excisions or destruction of the transformation zone are an important indicator for patients at risk of treatment failure or disease recurrence [6].

Since the great majority of women with high-grade CIN are of reproductive age [7], it is important to not compromise future pregnancies by surgical interventions on the cervix, which could be related to one of the most important causes of neonatal morbidity and mortality: preterm delivery (PD) [8, 9].
Several risk factors for spontaneous preterm birth have been suggested, but causal associations have been difficult to prove until now. Previous studies reported relations between surgical procedures for CIN and PD [9–11]; nevertheless explanations for this relation remain unclear [12]. Probably, the depth effect of surgical excision might explain discrepancies in the recent literature on the association between PD and prior treatment of cervical precancer lesions since different centers may have applied deep or less deep excisions.

Furthermore, cervical stenosis following excisional treatment for CIN has been reported more frequently among women who had long cones removed. Cervical stenosis has several potential adverse effects, including cervical factor infertility [13].

The primary aim of our study was to identify whether surgical excisional procedures for cervical intraepithelial neoplasia treatment are associated with increased risk of spontaneous preterm delivery (PD). The secondary outcome regarded the relation between these procedures and cervical factor infertility.

2. Materials and Methods

We performed a retrospective study using data collected from clinical records of patients who underwent surgical treatment for CIN at the Department of Obstetrics, Gynecology and Neonatology, University of Parma, from January 2005 to December 2011. Overall, 408 patients were treated in this timeframe.

We included in the cohort only patients in reproductive age (13–45 years) at time of the surgical procedures. Twenty-eight patients were excluded from the study on the basis of fertility status; 144 patients were excluded because they refused to answer the questionnaire and 236 patients were included in the study group.

Data collected regarded demographic features, gynecological and obstetric history and details about cervical procedure (CIN grade, surgical technique, and histopathology report) are reported in Table 1. We examined histopathology reports and for each patient we looked for the dimensions reported into the macroscopic description of the tissue removed. The height of the cone was the only feature considered, because this was comparable with the depth of the excision.

We interviewed patients to collect data about obstetrical history subsequent to cervical treatment: number of pregnancies, conception-to-conception interval, gestational age at delivery, and delivery modality. We also asked about diagnosis of secondary infertility caused by cervical stenosis.

On the basis of the information recorded we divided cases in two groups according to the gestational age at delivery: term delivery and preterm delivery (24–37 weeks). Only the first pregnancy after conization was taken into account. Statistics regarding features possibly related to PD (cone depth, timing between cervical surgery and pregnancy, and surgical technique) were performed with logistic regression. We used Student’s t-test to assess statistical differences between the mean heights of excision and relative standard deviation, (SD) for the two groups. Subsequently, we calculated the odds ratio (OR) with 95% confidence interval for a 1.5 cm cutoff (mean height of excision). Following this, a linear regression curve was elaborated.

Statistical analyses were performed by SPSS software 19 for Windows, using parametric and nonparametric tests when appropriate. The normality of the distribution was assessed by the Kolmogorov-Smirnov. Differences between two means were assessed with the Student’s t-test and associations between categorical variables were assessed with Pearson’s chi2 or the Fisher exact test.

Differences were considered statistically significant at $P < 0.05$.

3. Results and Discussion

3.1. Results. Among the 236 patients included, 56 (23.7%) conceived after the surgical procedure. Five of them decided to have abortion; four patients had a first-trimester spontaneous miscarriage; we did not report second-trimester miscarriages. Forty-seven women carried on pregnancy and delivered a viable fetus. None of the patients included in our study had a previous PD nor common risk factors for PD.

Ten patients delivered preterm: mild preterm delivery (from 32 to <37 weeks) occurred in 9 cases, whereas severe preterm delivery (28 to <32 weeks) only in 1 case. The mean gestational age at delivery was 35.07 (DS = 2.58) weeks for PD and 39.35 (DS = 1.08) weeks for term deliveries. There were 2 cases of induced preterm delivery and 8 cases of spontaneous preterm delivery; in our statistics we considered only spontaneous PD. Premature preterm rupture of membranes (P-PROM) occurred in 5 patients (62.5%); vaginal delivery was recorded in 40% of patients who delivered preterm and in 64.9% of women who delivered at term.

Concerning the interval time between the conization and pregnancy, we reported that only 1 case (12.5%) of PD occurred in patient who conceived within 12 months after cervical surgery, while the remaining 7 cases (87.5%) of PD in patients who conceived after 1 year from surgical treatment ($P = 0.04$). Regarding term delivery, 19 patients (51.4%) conceived before 1 year from cervical surgery while 18 ones (48.6%) conceived after 1 year from cervical treatment ($P = \text{n.s}$) (Table 1).

The mean cone depth was, respectively, 1.42 (DS = 0.47) cm and 1.82 (DS = 0.66) cm in patients with term and spontaneous PD (Table 2). We found a statistically significant relation ($P < 0.05$) between depth of the cone and gestational age (Figure 1). Student’s t-test showed a statistically significant difference ($P < 0.05$) between the mean depth of excision for the two study groups; we therefore demonstrated that the risk of preterm delivery is higher when cone depth exceeded a cutoff value of 1.5 cm (O.R. 7.14, 95% CI 1.37–37.228).

Concerning the relationship between surgical procedures for CIN and cervical factor infertility we observed that, among the 180 patients interviewed who did not get pregnant, 16 (8.8%) underwent hysterectomy and 5 (2.7%) underwent physiological menopause (i.e., absence of menses for at least 1 year with FSH serum value more than 30 IU). Three
patients (1.7%) declared secondary infertility caused by cervical stenosis (Table 3). In all cases there were a postsurgical hemorrhagic complication, resolved with suturing; in two of three cases the surgical procedure were performed with cold knife. On the basis of our data we could not find a relation between cervical stenosis and depth of excision.

3.2. Discussion. Our results showed that, after surgical treatment for CIN, particularly when the excision exceeded 15 mm in depth, the risk of PD is higher in women with deep versus less deep cones.

Sadler et al. [14] already demonstrated that for excisions of 17 mm or more the risk of pPROM but not of PD was higher.
Table 3: Infertile patients because of cervical stenosis.

| Case   | Histological diagnosis | Age | Surgical technique | Cone height (mm) | Parity | Complications of surgical treatment |
|--------|------------------------|-----|--------------------|-----------------|--------|-----------------------------------|
| 1      | CIN 3                  | 42  | Cold knife         | —               | 1      | Hemorrhagic complication           |
| 2      | CIN 3                  | 24  | LEEP               | 20              | 0      | Hemorrhagic complication           |
| 3      | CIN 3                  | 26  | Cold knife         | —               | 1      | Hemorrhagic complication           |

Figure 1: Linear regression curve shows the linear reverse correlation between gestational age at delivery (weeks) and height of exceeded cone (cm) ($P < 0.05$).

Our results suggest that surgical procedures for CIN increase the risk of spontaneous PD when the depth of the cone specimen exceeds 15 mm (OR = 7.143, 95% CI 1.37–37.228).

To avoid the malignant transformation of CIN and reduce the future pregnancies complications we therefore recommend to perform cone excision with a depth not more than 15 mm in women in reproductive age.

Conflict of Interests

All authors declare no conflict of interests.
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