Cervical Regeneration after Loop Electrosurgical Excision Procedure

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Cervical intraepithelial neoplasia (CIN) is a precursor of cervical cancer, and the most common CIN treatment is a loop electrosurgical excision procedure (LEEP). Advantages include patient compliance, outpatient setting, low cost, ease of learning for professionals, and availability of removed tissue for histological assessment, providing information on CIN severity and excision margins. At the same time, there are data that women after LEEP are predisposed to obstetrical complications including preterm birth. More efforts have to be made to study the pathogenic mechanism that leads to preterm birth.

Keywords: loop electrosurgical excision procedure (LEEP) ; cervical ; regeneration

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a precursor of cervical cancer, and the most common CIN treatment is a loop electrosurgical excision procedure (LEEP) [1]. Advantages of this include patient compliance, outpatient setting, low cost, ease of learning for professionals, and availability of removed tissue for histological assessment, providing information on CIN severity and excision margins [1][2].

There are reports that after LEEP and cold knife conization, women may have a higher risk of preterm delivery and second-trimester pregnancy losses [1]. There is a negative correlation between removed cones' dimensions after LEEP and the duration of pregnancy [3]. Studies that have precisely measured the removed cone's length and volume by ultrasound, fluid displacement technique, or measurements of the specimen concluded that cone length or volume can be evaluated by these methods interchangeably with precision [4][5].

The main theories about the pathogenesis of possible obstetrical complications include mechanical cervical defects, an altered barrier to ascending infections, and altered cervicovaginal microflora [6]. This implies that pathogenesis can be multifactorial and not only dependent on resected tissue dimensions or regeneration. The first theory is supported by Kyrgio et al., showing that pregnancy duration negatively correlates with increasing length of the cervix and volume of the resected cone [3]. There are alterations in vaginal microbiota following LEEP, resulting in less bacterial diversity and a reduction in the number of non-*Lactobacillus* bacterial species [6].

Nevertheless, all potential pathogenetic aspects should be taken into account, including the level of cervical regeneration and its impact on future pregnancies. Cervical tissues have the ability to regenerate from stroma and epithelial cells [7], but although authors speculate about the importance of the excised cone's proportions, cervical length, and volume regeneration capacities after LEEP, there are few data on how this regenerative process will impact later pregnancy complications.

The cervix morphology can be evaluated with several imaging techniques, such as CT scan, magnetic resonance, or ultrasound, performed either by transabdominal, transperineal, or transvaginal routes.

Transvaginal ultrasound has high image quality, low cost, and widespread availability. Plus, many studies have concluded that transvaginal ultrasound is a reliable tool for cervical measurements after the LEEP procedure.

Ricciotti et al., in 1995, was one of the first studies that reported a strong correlation between two-dimensional transvaginal cervical length measurement and ruler measurements of the excised cone length. Paraskevadis et al. concluded that excised cones' dimensions correlated well with transvaginally measured crater dimensions: diameter and height/depth. Dückelmann et al., with a strict and precise ultrasound measurement technique, showed a strong correlation between cone depth and transvaginal sonography measurements.

One of the flaws could be the variability between observers of measurement precision and image interpretation. Plus, there is a lack of data about three-dimensional cervical volume measurement precision. As pointed out, three-dimensional cervical volume measurements could have a subjective error due to differences in upper cervical border interpretation [8].

2. Cervical Regeneration after Loop Electrosurgical Excision Procedure

Cervical regeneration has been studied since 1995, and within these 25 years, studies have reached the conclusion that cervical regeneration occurs only partially, followed by potential obstetric complications.

Three studies examined regeneration until 6 months, and the study by Song et al. investigated regeneration until 12 months, concluding that cervical healing has no further regeneration after 6 months [9][10][11][12]. Only three studies investigated cervical volume regeneration [9][10][11]. All of them detected incomplete cervical volume healing 6 months after LEEP. Methods utilised for cervical volume measurements include Virtual Organ Computer-Aided Analysis (VOCAL) ultrasonography and cervical volume calculations with a cylinder formula.

The removed cone's depth and its proportion of cervical length and volume have predictive importance, as the risk of prematurity heightens with increases in the excised cone's depth. The Cochrane meta-analysis concluded that the relative risk (RR) for premature labour was 1.93 after excision of a cone with a length of 10–12 mm, 2.77 if the cone's length was 15–17 mm, and 4.91 if it was 20 mm or more [13].

The study by Papoutsis et al. concluded that if the excised cone's volume increases by 1%, then regeneration of tissue deficit at the cervical crater is reduced by 1.37%. Ciavattini et al. concluded that the removed cone's length and percentage of excised length had a negative correlation with cervical regeneration, but at the same time, no negative correlation with volume regeneration.

In studies, cervical volume was measured with two methods: three-dimensional ultrasound software (VOCAL) and by attributing cervical shape to a cylinder. Cylinder formula volume was calculated using two-dimensional measurements measuring cervical length, anteroposterior diameter (AP), and transverse diameter (LL). A comparison of both methods in a non-pregnant woman has been investigated in one study, which concluded that both methods have good agreement and a high degree of reliability (interclass correlation coefficient, 0.9; 95% confidence interval, 0.9–0.9) [14].

For clinical consideration, the two-dimensional ultrasound is cost-effective and more widely available than VOCAL software, allowing wider use of cervical volume measurements.

One of the factors that can contribute to different regeneration levels is the age of women under 25 years during LEEP. The LEEP procedure in women younger than 25 years can lead to overdiagnosis and excisional procedures on regressive, self-limiting CIN2 lesions [15]. Studies by Nicolas et al. and Papoutsis et al. included very young women under the age of 25 years, but Song et al. and Ciavattini et al.'s studies included women older than 25 years. Comparing younger women with older women, the former had lower regeneration levels (78.0%, 71.0% vs. 94.5%, 89.5%).

The relationship between cervical regeneration level and the excised cone's percentage of the cervix in the future could be used for premature labour risk stratification. It is clinically relevant to understand the sequence of cervical healing in women of reproductive age after the LEEP procedure. The knowledge can be used to develop evidence-based guidelines for screening and management of high-risk pregnancies.

After LEEP, there is a cervical regeneration deficit with completed healing 6 months after the procedure. There are insufficient high-quality studies that assess cervical volume regeneration and its relation to obstetrical outcomes. More research is needed to understand cervical regeneration capacity and define prenatal risks related to cervical regeneration.

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