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The Risk of Preterm Delivery Following Large Loop Excision of the Cervix: An Observational Cohort Study

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1. Abstract

Cervical intraepithelial neoplasia (CIN) is a precancerous condition common in women of reproductive age. The last decades the incidence of cervical neoplasia has decreased significantly. Important role has played the screening program amongst asymptomatic women. The aim of this retrospective study was to estimate the effect of LLETZ on pregnancy outcome among women that had been treated previously for CIN and compare these results with the pregnancy outcome among women with preterm delivery and without history of LLETZ. It appeals that women with previous LLETZ have increased risk of premature delivery by 1.5 times when they are compared with women without LLETZ in the past. The same group of women has increased risk of PROM too. Treated patients should be informed about increased risk of preterm births and the obstetricians/gynecologists should offer the most appropriate treatment to optimize the chances of a healthy pregnancy without compromising a woman's choices of treatment.

2. Introduction

Cervical intraepithelial neoplasia (CIN) is a precancerous condition common in women of reproductive age [1]. Over the past 30 years, the incidence of invasive cervical cancer has decreased markedly owing to far-reaching screening programs that have led to early diagnosis and treatment of cervical intraepithelial neoplasia (CIN) amongst asymptomatic women [2]. Effective treatment of high-grade lesions is important to prevent cervical cancer, and only a small proportion of low-grade lesions can and proceed to higher grades or invasive cancer [3, 4].

Women with abnormal cytology are referred to colposcopy for further assessment. In the United Kingdom, a majority of women with low grade cytology will either have no procedure (and be discharged) or have a punch biopsy sample taken at their first colposcopy appointment to confirm the presence or absence of disease, whereas others with high grade cytological abnormalities may be offered excisional treatment at the first visit [5].

Several techniques have been used in the treatment of pre-invasive lesions, such as cold-knife conization, laser ablation, laser conization, and loop electrosurgical excision procedure (LEEP), known also as Large Loop Excision of Transformation Zone (LLETZ) [6]. The last technique has become the standard treatment for women affected by cervical precancerous lesions, mainly based on its low rate of morbidity, the ability to define the margins of the excised tissue with a precise histologic diagnosis and the ability to combine diagnosis and therapy in an outpatient clinic [7].

The incidence of CIN peaks among women aged around 30 years of age, during their reproductive age; consequently, any possible effect of its treatment on future childbearing should be considered carefully [8]. An early report showed that there is an association between cold-knife conization and adverse obstetric outcomes,

including preterm delivery [9]. Subsequently, several systematic reviews and large retrospective studies have reported that women who have undergone LLETZ have a 1.7–3.7 fold increased risk of preterm delivery, low birth weight, and premature rupture of the membrane compared with untreated women [1,10-19]. The largest to date, a Norwegian record linkage study of 57 136 births before treatment and 15 108 after treatment, found the proportion of preterm deliveries in each group, respectively, to be 6.7% and 17.2% [20].

By contrast, there is limited data on the fertility and reproductive performance of women treated by LLETZ [21], Jakobsson et al. reported that there is not a strong association between cervical conization or ablation and subfertility [22].

Among women previously treated with LLETZ, cervical length is often monitored during the second trimester, but there is no preset reference value for this group of women. It is uncertain whether a precedent excision treatment leads to a permanent shortening of the cervix [23-25].

The aim of this study was to estimate the effect of LLETZ on pregnancy outcome among women that had been treated previously for CIN and compare these results with the pregnancy outcome among women with preterm delivery and without history of LLETZ.

3. Materials and Methods

A retrospective observational study was conducted in a tertiary center at three maternity units (Heartlands, Good Hope and Solihull Hospitals) from January 2015 to August 2020. Women with a single pregnancy were included. The women were then divided into two groups, those with a past history of one previous LLETZ, group "A" and group "B", women without previous cervical treatment. Women with risk factors for preterm birth, like a prior preterm delivery (<37 weeks) or mid-trimester miscarriage (>13 weeks) were excluded.

The national colposcopy database was used to identify the cohort of women who underwent treatment for CIN. These cases were linked to the Badger net (Electronic Maternity Record). The data linkage was performed by using the woman's unique identification number existing in both registers. The colposcopy database is supported and monitored by NHS England. All women having colposcopy are registered on the database.

The primary outcome was preterm birth before 37 weeks. Subgroup analysis was carried out to identify preterm delivery between 32 and 37weeks of gestation, 28 and 31 weeks and extremely preterm deliveries, less than 28-weeks of gestation.

A total of 746 pregnant women underwent an excisional cervical treatment (LLETZ) prior to their pregnancy were eligible and so included in our analysis. From these, 99 had had a premature delivery. These were compared with 5175 women that attended our maternity units, had premature delivery but didn't have any previous history of a LLETZ. Additionally, variables like maternal age at birth, body mass index, previous deliveries, birth weights, caesarean section as mode of delivery and maternal smoking during pregnancy for this particular group of women with premature births was analyzed. Finally, we ascertained the depth of loop excision tissue in cases with premature deliveries.

For the statistical analysis Graph Pad was used. Categorical variables were presented as frequencies and percentages. The categorical outcomes were presented as unadjusted odds ratios. As data was normally distributed continuous variables were presented as a mean with standard deviation and compared using student's test.

4. Results

Between 2015 and 2020, 55 324 women attended the Maternity Units across our three maternity sites for delivery. Over this five-year study period, the number of women who had a subsequent delivery following one large loop excision of the transformation zone (LLETZ) was 1.4%(746/55324), compared to 98.6% (54578/55324), who delivered without a history of LLETZ. Group A included the 99 out of 746 (13%) women with premature delivery and a LLETZ, while group B referred to 5157 women (9.4%), with premature births but no previous cervical treatment.

The main indication for LLETZ was CIN in histology results. More specifically, 72% of women had CIN3 at histology (537/746), followed by history of CIN2 in 14% of cases (102/746). Both inadequate colposcopy and CGIN were 7% each (52/746 and 52/746) of loops in the cohort of patients.

During the study period, women with history of LLETZ appeared to have 1.5 times an increased risk of preterm delivery compared to women (5157/55324) who did not have the treatment. Specifically, the risk for the first group is 13%, but for the second only 9% (OR 1.5 (95% CI 1.2 to 1.84). The risk of preterm birth in our treated women is twice the UK national data of preterm delivery in the general population (7%).

Of the 746 patients from the group A, 87/746 (12%) delivered between 24-37 weeks' gestation, whereas 12% (12/746) ended up with a 2nd trimester miscarriage (<24 weeks' gestation) (Table 1).

Women who underwent LLETZ were successful in achieving term delivery (≥37 weeks) in 85% (633/746), compared to 91% (49403/54578) women who had term delivery without a history of LLETZ during the same period. (OR 0.67, 95% CI 0.55 to 0.82).

We have studied the demographic characteristics and pregnancy outcome for the subgroup of women who had premature delivery, between group A and B (Table 2).

The subgroup analysis for the population with prematurity delivery shows that women who underwent LLETZ followed by subsequent delivery had a significantly higher mean age (36.1 years), and higher parity (2.6) compared with the rest, who had a mean age of (35.6 years), and parity of (2.4). They also had a signifi-

cantly higher body mass index (BMI). Demographics of the two groups of women who had preterm birth are summarized in (Table 2). This table also presents the mean birth weight for fetuses and it is obvious that the mean birth weight is lower for women with history of LLETZ treatment.

In our study women with preterm delivery, who underwent LLETZ treatment were nearly twice more likely to be smokers compared to women who delivered preterm with no history of LLETZ (12% vs 5%, P=<0.001). They appear to be less likely to have a delivery by caesarean section (42% vs 46%, P=<0.001) though (Table 2).

The mean depth of the loop for women in our population is 15 mm. Specifically, the mean loop depth for women who delivered between 32 and 37 weeks was 9mm, for these that delivered between 27 and 31weeks was 17mm. Women who delivered between 24 and 28 weeks had a mean loop depth 12mm and those with preterm delivery in the second trimester (13-24weeks) had a mean loop depth 22mm (Table 3).

Preterm rupture of membrane (PROM) occurred in 20% (20/99) of patients who had preterm delivery following a history of LLETZ. This is after excluding infection as a potential result for PPROM.

Table 1: Preterm delivery in women who had LLETZ compared to women who did not

Pregnancy outcome			
Time of delivery (in weeks)	**Deliveries with history of LLETZ (746)**	**Deliveries with no history of LLETZ (55324)**	**Statistical comparison**
32-37 (3rd Trimester)	59 (7.9%)	2254 (4.1%)	Odds ratio 2, 95% CI 1.55 to 2.66)
27-31(3rd Trimester)	13 (1.7%)	1400 (2.6%)	Odds ratio 1, 95% CI 0.41 to 1.25)
24-26 (2nd trimester)	15 (2%)	1267 (2.3%)	Odds ratio 0.9, 95% CI 0.55 to 1.54)
13-24 (2nd Trimester)	12 (1.6%)	254 (0.5%)	Odds ratio 3.7 (95% CI 2.04 to 6.75)
Total number of preterm deliveries	99 (13%)	5157 (9.4%)	Odds ratio 1.5 (95% CI 1.2 to 1.84)

Table 2: Characteristics of patients presenting with spontaneous preterm delivery

	Preterm deliveries with history of LLETZ (99)	**Preterm deliveries without history of LLETZ (5175)**	**Statistical comparison**
Patient characteristics			
Mean Age in years (SD)	36.1 (4.2)	35.6 (3.0)	P = <0.001
Mean Body mass index (SD)	32.8 (4.0)	27.1 (3.0)	P = <0.001
Mean Parity (SD)	2.6 (0.5)	2.4 (0.5)	P = <0.001
Mean birth weight in grams (SD)	3055 (650)	3445 (467)	P= <0.001
Caesarean section (%)	42 (42%)	2374 (46%)	P = <0.001
Smoking (%)	12 (12%)	245 (5%)	P = <0.001

Table 3: Loop depth in preterm deliveries

Time of delivery (in weeks)	**Deliveries with history of LLETZ (746)**	**Mean loop depth in mm (SD)**
32-37 (3rd Trimester)	59 (7.9%)	9 (7)
27-31(3rd Trimester)	13 (1.7%)	17 (11)
24-26 (2nd trimester)	15 (2%)	12 (8)
13-24 (2nd Trimester)	12 (1.6%)	22 (17)
Total number of preterm deliveries	99 (13%)	15 (10)

5. Discussion

LLETZ is a safe and effective method for the treatment of CIN. LLETZ is classified as a technique with minimal diathermy damage of surrounding tissue, minimal bleeding, simple procedure, minimal invasion, short operative time and low cost. It has already been acknowledged that the specimens obtained by LLETZ are significantly smaller and contain less of the cervical canal when it is compared with conization [26, 27].

As we know, connective tissue, smooth muscle, blood vessels, and elastic fibers, which comprise the cervix, are considered to play an important role in pregnancy and delivery. Excessive tissue excision leads to a loose cervix or cervical incompetence, which can result in a higher rate of premature birth, miscarriage and also increases the risk of infection. Some bacteria associated with preterm birth, such as Bacteroides fragilis and group B Streptococcus, release phospholipase A2 or proteolytic enzymes associated with uterine contractions and premature rupture of the membranes [28].

Some studies reported that women affected by CIN could have a tendency to a higher frequency of health problems when compared to the general population because of lifestyle choices. Consequently, their increased risk of preterm delivery might be related to these factors [25, 29, 30].

Our study indicated smoking habits is a significant predictive risk factor of preterm delivery among the treated women. This could be due to the fact that smoking plays a role in persistence of HPV infection through the impairment of the immune syste [31]. There is agreement that treated women are more likely to experience a preterm delivery not only due to the loss of cervical tissue with the decreased mechanical support that it provides [1, 10, 19-23] but also for the changes in the immune system [21] and altered vaginal environment of women during pregnancy [32]. These changes play a very important role by promoting the persistence of HPV, favoring the development of frequent ascending infections and consequent premature labour and delivery.

In our study, we observed that women with a second trimester delivery had the loop with the biggest mean depth. Paradoxically women with preterm labour between 27 and 31 weeks had a loop with bigger mean depth than women who had delivery between 24 and 26 weeks. There are studies reporting similar information; which proves that the depth of the loop excision itself can't predict the severity of prematurity [12, 18]. There are more factors than the cervical length to define the outcome of a pregnancy and further study is necessary in order to understand the physiology and identify all the factors involved.

There is consensus that the incidence of premature births increases with the depth of excision. The latest review by Kyrgiou et al. [38] reports a 1.54 risk of preterm delivery when the depth of the loop 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 [38]. Our study also confirms that depth of treatment is a statistically significant risk factor for preterm birth. The risk was increased for excisions more than 12 mm in depth. It has 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 [39].

In our study, 20% of women with history of previous LLETZ and premature delivery developed PROM. In this group of study women with history of any kind of infection had been excluded, since infection is recognized as a main reason for PROM [10]. Literature agrees that women with LLETZ have a 2 fold (6.1%) higher risk of PROM, while without LLETZ it is only 3.4% [40].

One of the strengths of this study is the fact that data have been collected through the national colposcopy database and the local electronic system "badger net". As result, is very unlikely to miss or get inaccurate data. The retrospective type of this study is one of its limitations. In addition, if women with previous LLETZ had a preterm birth in a different hospital, won't be included in our data. However, it is unlikely we missed a statistically significant number

of patients given the fact that all maternity hospitals in Birmingham use the same electronic maternity system (Badger net). Similarly, the risk of missing any pregnancy complication relevant to the loop like PPROM should be negligible.

We did not adjust our analyses for potential confounding variables because extensive clinical and demographic data were not electronically recorded over the study period.

The findings of previously published meta-analyses are discordant, as the parameters compared were different when analyzing the depth of excision associated with the treatment techniques, and the quality of the meta-analyses themselves [18, 33-38].

The cervix has been traditionally considered to regenerate rapidly. Treatments for CIN are considered safe, easy, without impairing pregnancy outcomes. However, the procedure of LLETZ clearly predisposes to preterm birth. We found almost a two-fold risk for preterm birth after LLETZ by using internal controls. Human papillomavirus infections are increasing, and women conceive and deliver when older, which translates into increasing numbers of parturient with a history of LLETZ. Therefore, unnecessary "see and treat" procedures should be avoided.

6. Conclusion

Our data confirm that women who have undergone excisional treatment for CIN2 and above have an increased risk of preterm delivery and PROM. We could identify smoking as an important impact factor that 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 a woman's choices of treatment. We propose that there is a need for multicenter studies making it possible to calculate a "risk score". This could potentially provide women with personalized risk assessments to support physicians offering adequate counselling concerning the potential obstetric sequelae of a cervical excision.

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