Impact of past obstetric history and cervical excision on preterm birth rate

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Abstract
Introduction: To determine the impact on preterm birth (PTB) of a history of large loop excision of the transformation zone (LLETZ)-alone compared with a history of previous preterm birth-alone (PPTB) or a history of both (LLETZ+PPTB). Secondary analyses were performed to evaluate the impact of antenatal interventions, depth of cervical excision, and patient risk factors on PTB rate in each cohort.

Material and methods: A retrospective observational cohort study of women referred to a tertiary Antenatal Prematurity Prevention Clinic with a history of LLETZ, PPTB, or LLETZ+PPTB. Information was collated from routinely collected clinical data on patient demographics, previous obstetric history, LLETZ dimensions, antenatal investigations/interventions, and gestation at delivery.

Results: A total of 1231 women with singleton pregnancies were included, 543 with history of LLETZ-alone, 607 with a history of PPTB-alone and 81 with a history of LLETZ+PPTB. PTB rates were 8.8% in the LLETZ-alone group, which mirrored the PTB rate in the local background obstetric population (8.9%) compared with 28.7% in the PPTB-alone and 37.0% in the LLETZ+PPTB cohorts. PTB rates were higher in LLETZ cohorts treated with antenatal intervention (cervical cerclage or progesterone pessary) and there was no evidence of an effect of intervention on risk of PTB in post-excision patients with identified shortened mid-trimester cervical length. Logistic regression modeling identified PPTB as a strong predictor of recurrent PTB. Excision depth was correlated with gestation at delivery in the LLETZ-alone group \((r = -0.183, p < 0.01)\) although this only reached statistical significance at depths of 20 mm or more (odds ratio [OR] 3.40, 95% CI 1.04–1.11, \(p = 0.04\)). Depth of excision was not correlated with delivery gestation in the LLETZ+PPTB group \((r = -0.031, p = 0.82)\).

Conclusions: PPTB has a greater impact on subsequent PTB risk compared with depth of cervical excisional treatment. The value and nature of antenatal interventions should be investigated in the post-excision population.

Abbreviations: CIN, cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone; OR, odds ratio; PPC, prematurity prevention clinic; PPTB, previous preterm birth; PTB, preterm birth.
Adverse obstetric outcomes, such as preterm birth (PTB), are associated with excisional treatments for cervical intraepithelial neoplasia (CIN). Meta-analysis of cohort studies has identified treatment factors that increase PTB risk, including type of excisional treatment, the number of excisions and increasing cone depth or volume. However, the included studies in these meta-analyses have been subject to inherent bias, particularly the failure to control for founders of key outcomes. For example, women with CIN have a higher baseline risk of PTB, irrespective of whether they have undergone treatment, and HPV vaccination is reported to be associated with a reduction in the relative rate of preterm birth. The impact of previous preterm birth (PPTB), a known risk-factor for subsequent PTB, has not been fully investigated in post-excision populations and may confound key outcomes when assessing the relation between cervical excision and PTB.

The introduction of specialist prematurity prevention clinics (PPC) into mainstream obstetric practice has concentrated the antenatal care of women at high-risk of PTB providing a useful resource to evaluate specific patient populations to define optimal antenatal management. Despite an evidence base for many preventive therapies, such as cervical cerclage and progesterone pessaries, in a general obstetric population at risk of PTB, in post-excision populations it is unknown to what extent antenatal interventions improve obstetric outcomes. Several retrospective cohort studies and a recent meta-analysis have reported non-significant higher odds of PTB in post-excision patients treated with cerclage compared with expectant management; however, interpretation is limited by confounding due to the higher frequency of shortened cervical length and PPTB in cerclage groups. There is only a single small randomized controlled trial comparing vaginal progesterone therapy to cervical cerclage in post-excision patients, which reported no significant differences in overall PTB rates unless the cervical length was 15 mm or less when cerclage was favored.

We therefore performed a retrospective cohort study to investigate the PTB rate in women who had previously undergone cervical excisional treatment compared with women who had a non-excision associated history of PTB and women with a combination of both, under the care of a specialist prematurity prevention clinic. Outcomes were compared between patients who received supportive care and surveillance only with those who received antenatal intervention (cerclage or progesterone) to prevent PTB.

This was a historical cohort study of routinely collected clinical data with the primary aim of evaluating PTB rates in women with a history of cervical excision alone, a history of PPTB-alone or a combined history of both excision and PPTB. These data were collected for women referred to a single tertiary PPC (University Hospitals of Leicester NHS Trust) between 2009 and 2016.

### Key message
Previous preterm birth has a greater impact on subsequent risk of preterm birth compared with cervical excisional treatment.
PPTB-alone or a history of both LLETZ+PPTB. Secondary analyses were performed to evaluate the impact of prophylactic antenatal interventions on PTB rate in a LLETZ population and the impact of depth and number of cervical excisions, patient demographics, smoking status, and body mass index on PTB rate.

### 2.4 | Statistical analyses

Statistical analyses were performed using R version 3.6.1. Rates of PTB before 37 weeks of gestation (all preterm birth) and before 34 weeks of gestation (early preterm birth) were estimated for all groups. Univariate and multivariate logistic regression analysis was performed to evaluate risk factors for PTB with a $p$ value less than 0.05 used to determine nominal statistical significance. Further logistic regression modeling was performed to compare the effect of intervention vs surveillance only on PTB rates in LLETZ patients with short cervical length ($\leq$25 mm) at the mid-trimester transvaginal ultrasound scan, using the surveillance group as an internal control. The 25-mm cut-off was selected as this is recommended to select patients for treatment in national guidelines. To assess if there was a relation between parity and risk of PTB in the LLETZ population, the rate of PTB within nulliparous and multiparous groups with no previous history of PTB was estimated and a two-sample test for equality of proportions was performed. Logistic regression modeling with preterm delivery as the outcome and combined cervical depth as the predictor was used to evaluate the relation between depth of cervical excision and gestation at delivery. The odds ratio (OR) for the increase in odds of PTB per millimeter of excision depth was calculated. Mean delivery gestation for each depth category (1–9, 10–14 15–19, and 20 mm or more) was compared with the Student’s $t$ test between LLETZ and LLETZ+PPTB groups. In addition, Pearson’s correlation coefficient was calculated to assess the correlation between depth of excision and gestation at delivery. Logistic regression of PTB on total number of previous LLETZ was performed.

### 2.5 | Ethical approval

Approval for the study was given by the University Hospitals of Leicester Clinical Audit team (Study registration number: 6747) on October 10, 2016.

### 3 | RESULTS

In total, 1383 women were referred to the PPC during the study period. Excluding the “other” referral indication category produced a total of 1231 singleton pregnancies of which 624 women had previously undergone at least one cervical excision; 543 women were referred due to a history of LLETZ-alone, 607 patients were referred with a history of PPTB-alone and 81 women were referred because of a history of LLETZ+PPTB. Demographic characteristics for each cohort are displayed in Table 1. In the PPTB-alone cohort, there was a higher proportion of women of Asian/Black ethnicity and higher BMI whereas in the LLETZ+PPTB cohort, there was a higher

| TABLE 1 | Maternal characteristics of included patients for each cohort |
|----------|----------------------------------------------------------|
|          | LLETZ-alone ($n=543$) | PPTB-alone ($n=607$) | LLETZ+PPTB ($n=81$) |
| Age (years) Median (range) | 31.3 (21–46) | 29.6 (15–46) | 31.6 (22–42) |
| Ethnicity, $n$ (%) | | | |
| | White | 514 (94.7) | 407 (67) | 76 (93.9) |
| | Asian | 13 (2.4) | 104 (17.1) | 1 (1.2) |
| | Black | 6 (1.1) | 63 (10.4) | 3 (3.7) |
| | Chinese | 1 (0.2) | 1 (0.2) | 0 (0) |
| | Other | 9 (1.6) | 32 (5.3) | 1 (1.2) |
| Parity, $n$ (%) | | | |
| | Nulliparous | 307 (56.5) | 0 (0) | 0 (0) |
| | Multiparous | 236 (43.5) | 607 (100) | 81 (100) |
| Smoking status, $n$ (%) | | | |
| | Smoker | 162 (29.8) | 176 (29) | 37 (45.7) |
| | Non-smoker | 381 (70.2) | 431 (71) | 44 (54.3) |
| Body mass index (kg/m$^2$), $n$ (%) | | | |
| | $<18.5$ | 9 (1.7) | 32 (5.3) | 3 (3.7) |
| | 18.5–24.9 | 251 (46.2) | 235 (38.7) | 40 (49.4) |
| | 25–30 | 184 (33.9) | 163 (26.9) | 23 (28.4) |
| | 30–34.9 | 57 (10.5) | 92 (15.1) | 8 (9.8) |
| | 35–39.9 | 29 (5.3) | 48 (7.9) | 3 (3.7) |
| | $>40$ | 3 (0.6) | 21 (3.5) | 2 (2.5) |
| | Not recorded | 10 (1.8) | 16 (2.6) | 2 (2.5) |
| Cerclage, $n$ (%) | | | |
| | History indicated | 4 | 70 | 8 |
| | Ultrasound indicated | 19 | 69 | 4 |
| | Existing trans-abdominal | | | 1 |
| | Not recorded | 1 | 1 | – |
| Vaginal progesterone, $n$ (%) | | | |
| | $<14$ | 14 (2.6) | 28 (4.6) | 8 (9.9) |
| | $\geq 14$ | 6 (1.1) | 10 (1.6) | – |

Note: The proportion of women who underwent each prophylactic antenatal intervention is displayed alongside the indication for cervical cerclage. History-indicated or elective cerclage were inserted following local expert recommendation due to a past obstetric history of preterm birth, multiple previous cervical excisions or previous cerclage. Women treated with ultrasound-indicated cerclage were offered cerclage following ultrasound evidence of shortened cervical length $\leq$25 mm in the second trimester.
proportion of smokers compared to the other cohorts. Two hundred and twelve of the 1231 patients (17.2%) received a prophylactic antenatal intervention. 178 women were treated with cervical cerclage, and 50 women were prescribed progesterone pessaries; of these, 16 women were treated with combined cervical cerclage and progesterone therapy. Table 1 displays the distribution of antenatal interventions across the three patient cohorts and the indication for cervical cerclage in each group. The total depth of cervical excision was available in 489 women, of whom 418 had had a single LLETZ, 63 had had two previous LLETZ and eight had had three previous LLETZ.

Mean gestation at delivery was 276 days (39.4 weeks) in the LLETZ-alone cohort, 261 days (37.3 weeks) in the PPTB-alone cohort, and 257 days (36.5 weeks) in the LLETZ+PPTB cohort. Comparing groups there were statistically significant differences in gestation at delivery between the LLETZ-alone and PPTB-alone groups (difference 15.51 days; 95% CI 12.85–18.16 days; p < 0.01) and the LLETZ-alone and LLETZ+PPTB groups (difference 18.74 days; 95% CI 12.64–24.65 days; p < 0.01), but not when comparing the PPTB-alone with LLETZ+PPTB groups (difference 3.24 days; 95% CI −3.20 to 9.68 days; p = 0.32). In all, 91.2% of LLETZ-alone women delivered after 37 weeks compared with 71.3% in the PPTB-alone cohort and 63.0% in the LLETZ+PPTB cohort. Two hundred and fifty-two of the included participants had a PTB, 104 of which were delivered before 34 weeks of gestation. PTB rates in each cohort were as follows: LLETZ-alone, 8.8% overall PTB rate with a 2.6% early (<34 weeks) PTB rate compared with 28.6% and 13.0% in the PPTB-alone group and 37.0% and 13.6% in the LLETZ+PPTB group, respectively (Figure 1). PTB rates in the LLETZ-alone group were comparable with the local PTB rate of 8.9% in the unselected background Leicester population in 2016.

Of the 252 PTB in the study period, 192 occurred in women who were monitored with antenatal surveillance-alone at the PPC during their pregnancy and 60 occurred in women who were treated with a prophylactic obstetric intervention. Of these births, 104 deliveries were before 34 weeks of gestation, 78 of which were in the surveillance group and 26 in the intervention group. PTB rates in the surveillance cohort were as follows; LLETZ-alone 8.4% at less than 37 weeks of which 2.3% were at less than 34 weeks compared with 29.2% and 13.4% in the PPTB-alone group and 30.0% and 10.0% in the LLETZ+PPTB group, respectively. In the intervention cohort, PTB rates were as follows; LLETZ-alone 15.6% overall, of which 6.3% were before 34 weeks compared with 27.0% and 11.9% in the PPTB-alone group and 57.1% and 23.8% in the LLETZ+PPTB only group, respectively.

Comparing PTB rates between intervention and surveillance cohorts was statistically significant in the LLETZ+PPTB cohort before 37 weeks of gestation (p = 0.04) but not before 34 weeks of gestation. There were no statistically significant differences between PTB rates comparing intervention and non-intervention cohorts in the LLETZ-alone group for delivery before 37 weeks or before 34 weeks of gestation, although the increase in PTB rate from 8.4% to 15.6% may be clinically significant. There were no statistically significant differences in PTB rates between intervention and surveillance cohorts in the PPTB group for delivery at less than 37 weeks or at less than 34 weeks.

Preterm birth rates in patients with both a history of cervical excision (LLETZ and LLETZ+PPTB cohorts) and shortened cervical length (≤25 mm) at mid-trimester transvaginal ultrasound scan in the index pregnancy were compared between women who received antenatal intervention (n = 78) and those who were monitored with surveillance only (n = 120). In the intervention cohort, 26 women (33.3%) delivered at less than 37 weeks of gestation, 8 (10.3%) of whom delivered at less than 34 weeks of gestation. In the surveillance cohort, 40 women (33.3%) delivered at less than 37 weeks of gestation, 16 (13.3%) of whom delivered at less than 34 weeks of gestation. Comparing groups, among post-excision patients with cervical length up to 25 mm, there was no evidence of an effect of intervention on risk of PTB before 37 weeks of gestation (OR 1.00, 95% CI 0.55–1.83) or before 34 weeks of gestation (OR 0.74, 95% CI 0.30–1.83).

Univariate and multivariate logistic regression modeling identified PPTB as a strong risk factor for PTB for delivery at both less than 37 and less than 34 weeks of gestation across all cohorts (Table 2). In the surveillance population (n = 571), PPTB was the only significant predictor of PTB at any gestation, with an OR of 4.04 (95% CI 2.08–7.86, p < 0.01) for delivery at less than 37 weeks and OR 4.66 (95% CI 1.46–14.9 p = 0.01) for delivery at less than 34 weeks. Comparing this with the intervention population (n = 53), a history of PPTB conferred an OR of 21.5 (95% CI 2.35–197, p < 0.01) for delivery at less than 37 weeks, which decreased to 3.39 (95% CI 0.44–26.1, p = 0.24) for delivery before 34 weeks; however, the confidence intervals were broad because of the low number of events in this population. No statistically significant difference in PTB rate was detected between nulliparous and multiparous women with no previous history of PTB following LLETZ.

A history of smoking was independently associated with PTB when evaluating all included patients (OR 1.65, 95% CI 1.16–2.21, p < 0.01). The association was weaker when considering PTB at less than 34 weeks of gestation (OR 1.28, 95% CI 0.80–2.05, p = 0.31) probably owing to the reduced number of events. There was no
TABLE 2  Univariate and multivariate analysis of risk factors for preterm birth at before 37 weeks and before 34 weeks of gestation for all patients as well as for patients with a history of LLETZ who were treated with supportive care and surveillance-alone (n = 565) or patients with a history of LLETZ who were treated with an antenatal intervention; cervical cerclage, progesterone pessaries or combined treatment (n = 59)

| Independent variable | Univariate OR (95% CI), p value | Multivariate OR (95% CI), p value |
|----------------------|---------------------------------|----------------------------------|
|                      | <37 weeks, n = 252              | <34 weeks, n = 104               | <37 weeks, n = 252              | <34 weeks, n = 104               |
| Smoking              |                                  |                                 |                                 |
|                      |                                 |                                 |                                 |
| Smoking              | 1.68 (1.26–2.25) p < 0.01      | 1.41 (0.93–2.14) p = 0.10       | 1.65 (1.16–2.21) p = 0.01       | 1.28 (0.80–2.05) p = 0.31        |
| PPTB                 | 4.35 (3.1–6.1) p < 0.01        | 5.69 (3.2–10.1) p < 0.01        | 4.55 (3.02–6.49) p < 0.01       | 5.17 (2.85–9.38) p < 0.01        |
| BMI                  | 0.99 (0.96–1.01) p = 0.38      | 0.98 (0.94–1.02) p = 0.35       | 0.98 (0.96–1.01) p = 0.26       | 0.97 (0.94–1.01) p = 0.16        |
| Age                  | 0.98 (0.95–1.00) p = 0.09      | 0.96 (0.93–1.00) p = 0.07       | 1.00 (0.97–1.03) p = 0.86       | 0.98 (0.95–1.02) p = 0.42        |

LLETZ no intervention

| Independent variable | Univariate OR (95% CI), p value | Multivariate OR (95% CI), p value |
|----------------------|---------------------------------|----------------------------------|
|                      | <37 weeks, n = 61              | <34 weeks, n = 18               | <37 weeks, n = 61              | <34 weeks, n = 18               |
| Smoking              |                                 |                                 |                                 |
| Smoking              | 1.37 (0.79–2.38) p = 0.26      | 0.84 (0.29–2.39) p = 0.74       | 1.18 (0.65–2.13) p = 0.59      | 0.52 (0.15–1.74) p = 0.29       |
| PPTB                 | 4.64 (2.47–8.80) p < 0.01     | 4.62 (1.67–12.8) p < 0.01      | 4.04 (2.08–7.86) p < 0.01      | 4.66 (1.46–14.9) p < 0.01       |
| BMI                  | 0.94 (0.88–1.01) p = 0.08     | 0.93 (0.82–1.06) p = 0.27     | 0.95 (0.89–1.01) p = 0.09     | 0.93 (0.83–1.06) p = 0.29       |
| Age                  | 1.01 (0.95–1.08) p = 0.67     | 0.94 (0.84–1.06) p = 0.30     | 1.02 (0.96–1.09) p = 0.55     | 0.93 (0.82–1.05) p = 0.21       |

LLETZ with intervention

| Independent variable | Univariate OR (95% CI), p value | Multivariate OR (95% CI), p value |
|----------------------|---------------------------------|----------------------------------|
|                      | <37 weeks, n = 17              | <34 weeks, n = 7                | <37 weeks, n = 17              | <34 weeks, n = 7                |
| Smoking              |                                 |                                 |                                 |
| Smoking              | 2.55 (0.78–8.38) p = 0.12     | 0.62 (0.11–3.56) p = 0.59       | 11.6 (1.26–107) p = 0.03      | 0.80 (0.10–6.24) p = 0.83       |
| PPTB                 | 7.2 (1.99–26.1) p < 0.01     | 4.69 (0.82–26.9) p < 0.01      | 21.5 (2.35–197) p < 0.01      | 3.39 (0.44–26.1) p < 0.01       |
| BMI                  | 0.82 (0.71–0.96) p = 0.01    | 0.76 (0.60–0.97) p = 0.02     | 0.86 (0.72–1.03) p = 0.09     | 0.78 (0.61–1.01) p = 0.06       |
| Age                  | 1.02 (0.87–1.20) p = 0.79    | 1.05 (0.84–1.33) p = 0.67     | 1.02 (0.82–1.27) p = 0.86     | 0.97 (0.73–1.29) p = 0.82       |

Abbreviations: BMI, body mass index; LLETZ, large loop excision of the transformation zone; OR, odds ratio; PPTB, previous preterm birth.

effect of age, ethnicity or body mass index on PTB across any cohort (Table 2). Numerical data for each variable across term and preterm deliveries is provided in Table S1.

Increasing depth of cervical excision, (n = 489) was negatively correlated with gestation at delivery (r = −0.14, p < 0.01) indicating an association between increased depth of cervical excision and earlier delivery. The mean gestation at delivery was at term in all depth categories (Table 3). Odds ratios for PTB before 37 weeks of gestation and before 34 weeks of gestation by depth category are reported in Table 3 using 1–9 mm as a reference population. A statistically significant increase in PTB rate was only demonstrated at excision depths of 20 mm or more (OR 3.40, 95% CI 1.04–11.11, p = 0.04).

In the LLETZ-alone cohort (n = 430) there was a statistically significant negative correlation between depth of excision and delivery gestation (r = −0.18, p < 0.01). In the LLETZ+PPTB cohort (n = 59) there was no statistically significant correlation between excision depth and delivery gestation (r = −0.03, p = 0.82). Mean delivery gestation was compared for each depth category between the LLETZ-alone and LLETZ+PPTB cohorts. Delivery gestation was reduced in the LLETZ+PPTB cohort at depths of 1–9 mm (p < 0.01), 10–14 mm (p < 0.01), and 15–19 mm (p < 0.01). There was no difference in mean delivery gestation between LLETZ-alone and LLETZ+PPTB groups at depths of 20 mm or more (p = 0.09).

Total number of cervical excisions (one previous, two previous or three previous) was not associated with significant differences in PTB rate in either the LLETZ-alone cohort (chi-squared 3.83, p = 0.15) or the LLETZ+PPTB cohort (chi-squared 2.14, p = 0.34).
TABLE 3 The proportion of preterm births are displayed for each depth category for women with a history of LLETZ

| Depth (mm) | n = no. of patients | <34 weeks gestation, n (%) | 34–36+ weeks gestation, n (%) | ≥37 weeks gestation, n (%) | Mean gestation at delivery (days, weeks) | Delivery <37 weeks gestation OR (95% CI) p-value | Delivery <34 weeks gestation OR (95% CI) p-value |
|-----------|------------------|----------------------|---------------------------|----------------------|---------------------------------|---------------------------------|---------------------------------|
| 1–9 (n=36) | 3 (8.3) | 1 (2.7) | 32 (88.9) | 269.2, 38+3 | — | — | — |
| 10–14 (n=275) | 5 (1.8) | 21 (7.7) | 249 (90.5) | 275.9, 39+3 | 0.84 (0.27–2.55) | p = 0.75 | 0.20 (0.05–0.89) | p = 0.04 |
| 15–19 (n=121) | 9 (7.4) | 14 (11.6) | 98 (81.0) | 270.9, 38+5 | 1.88 (0.60–5.84) | p = 0.28 | 0.88 (0.23–3.45) | p = 0.86 |
| ≥20 (n=57) | 4 (7.0) | 13 (22.8) | 40 (70.2) | 266.3, 38+0 | 3.40 (1.04–11.11) | p = 0.04 | 0.83 (0.18–3.95) | p = 0.82 |

Note: In women with multiple excisions, the depth measurements from each excision were added to give an overall depth measurement, which was then used to categorize each patient. Mean gestation at delivery is displayed in days and weeks for each depth category.

Abbreviations: LLETZ, large loop excision of the transformation zone; OR, odds ratio.

4 | DISCUSSION

We have identified that the risk of PTB associated with a previous LLETZ for CIN in women with no personal history of PTB mirrored the rate in our background obstetric population, 8.8% and 8.9%, respectively. In contrast, a history of PPTB carried significantly greater risk of subsequent PTB and the addition of LLETZ to this did not significantly increase this rate, suggesting that a history of PPTB has a far greater impact on delivery gestation than a history of LLETZ-alone. PTB rates were higher in post-excision populations treated with prophylactic antenatal intervention, although this difference did not reach statistical significance and in post-excision patients with identified shortened mid-trimester cervical length there was no evidence of an effect of intervention on risk of PTB. A negative correlation between depth of excision and delivery at gestation was identified although this only reached statistical significance at depths of 20 mm or more. The mean delivery gestation was longer than 37 weeks of gestation across all the depth groups, including 20 mm or more.

Strengths of our study include the large sample size, appropriate comparator groups to control for PPTB, and detailed pathological data available for LLETZ procedures. However, this was a retrospective study with risk of selection bias. Our comparison group consisted of high-risk pregnancies, which is not representative of a general obstetric population, therefore our results cannot be extrapolated to low-risk groups and should only be viewed in the context of providing risk-stratification and counseling for known high-risk patients within a specialist PPC. Use of antenatal interventions may have confounded the primary outcome therefore we displayed results for all included patients in each cohort and for surveillance and intervention groups separately to assist with interpretation. The PTB rate in our background population is slightly higher than the UK rate, 7-8% since 2010, which may be attributed to increased risk factors within the local population or data collection errors. 18

Although existing evidence surrounding the relation between excisional treatments for CIN and PTB confirms an association, measures of magnitude of the effect have been inconsistent and wide-ranging. 3,5 Importantly, information regarding previous obstetric history of preterm delivery in the included study populations has often been absent. Study populations have included retrospective cohorts with variable control groups, in particular, the use of external historical controls, which may have resulted in overestimation of effect size, 19 and defining a comparator group has proven challenging. Comparing patients with previous LLETZ to a low-risk obstetric population fails to consider obstetric confounders. In this study we identified that a history of PPTB significantly increases the risk of PTB in patients with a history of cervical excision and is likely to have acted as a confounder of primary outcomes if not controlled for in previous studies.

In our study, patients with a history of LLETZ-alone had the lowest overall rates of PTB (8.8%), particularly at less than 34 weeks (2.6%) and this was comparable to our background reference population (8.9%). In the LLETZ-alone cohort, the majority of preterm deliveries (70.8%) were between 34 and 36 weeks where neonatal outcomes are much improved compared with delivery at earlier gestations, similar to findings by Maina et al, where 88.7% of PTB in a LLETZ population were delivered at this gestation. 20 This is in contrast to Poon et al who identified LLETZ as an independent risk factor for both early (OR 3.02) and late (OR 1.79) PTB after adjusting for maternal characteristics including ethnicity, smoking, and PPTB. 21

fitting the same logistic regression model to our data yields the corresponding OR of 1.00 (95% CI 0.94–1.07) and 1.07 (95% CI 0.96–1.16). This discrepancy may be explained as the Poon et al cohort were receiving routine antenatal care compared with our population who received care in a designated PPC, which may have reduced the risk of PTB. Knowledge that in the absence of PPTB, a post-excision population has a low overall preterm birth rate, particularly at early gestations when the neonatal impact is greatest, is likely to reassure women with a history of LLETZ and enable treating clinicians in PPCs to be optimistic regarding likely outcomes when counseling women.

Previous PTB was the most significant independent risk factor for PTB in the LLETZ population. PPTB is an established risk factor for recurrent PTB with any history of term delivery acting as a protective factor. 22 Our findings are consistent with this, identifying that the addition of LLETZ did not significantly increase the risk of PTB in women with a history of PPTB and there was no statistically
significant increase in PTB risk after LLETZ procedures for multiparous women with previous term deliveries. This suggests that it is the history of PPTB, rather than the LLETZ, that confers the greatest risk.

In our study there was an increase in preterm delivery rates in LLETZ-alone and LLETZ+PPTB patients who had a prophylactic obstetric intervention compared with women who received surveillance only. This was only statistically significant in the LLETZ+PPTB group, which likely reflects the higher number of outcome rates in this group; however, these findings may be of clinical importance because they suggest a lack of efficacy in post-excision patients undergoing intervention. Our subgroup analysis of patients with a history of cervical excision and shortened mid-trimester cervical length did not find evidence of an effect of intervention on PTB rate. There are inherent differences in PTB risk between women who meet criteria for obstetric intervention (PPTB, previous cerclage, evidence of mid-trimester shortened cervical length) compared with those who do not, which may confound the primary outcome. PPCs have been shown to accurately risk-stratify asymptomatic high-risk women into those who ultimately deliver preterm and those who do not. Therefore, the higher rates of PTB in patients receiving an intervention may simply reflect appropriate selection and treatment of the highest risk women. Nevertheless, in women with a history of PPTB-alone, there were no statistically significant differences in outcomes noted between intervention and surveillance groups, which may indicate that interventions have more success in preventing PTB in higher risk groups in non-excision populations.

Evidence for the efficacy of prophylactic interventions in post-excision groups is lacking with several small retrospective cohort studies failing to demonstrate therapeutic benefit of cervical cerclage, and only a single study comparing cerclage to progesterone, which found no evidence for the superiority of either intervention. A recent study has shown that choice of suture material may improve outcomes in post-excision populations with a lower PTB rate demonstrated following insertion of monofilament compared with braided suture. There is significant heterogeneity in intervention-use within PPCs and a lack of standardized management protocols makes designing randomized controlled trials to evaluate these interventions challenging, particularly when multiple interventions are used in highly variable patient groups with significant risk of confounding and bias. Data from observational studies conducted in PPCs are therefore highly valuable for informing practice and may help to stratify which interventions are most effective for specific patient groups or for identifying where trials would be most beneficial.

Increased depth of cervical excision did correlate with an increased risk of preterm birth, as has been demonstrated in previous studies, and was statistically significant at depths of 20 mm or more. Noehr et al., who evaluated 8180 deliveries in the Danish population after cervical excision, identified preterm birth rates of 5.3% (OR 1.00) for excisions less than 12 mm, 4.4% (OR 0.82) at 13–15 mm, 7.2% (OR 1.44) at 16–19 mm excisions, and 9% (OR 1.76) for excisions of 20 mm or more. Furthermore, Castanon et al., demonstrated that small excisions, particularly less than 10 mm, had a minimal effect on risk of PTB (7.5% PTB rate), with a doubling in risk of preterm birth seen with larger excisions 15 mm of more in depth (15.3% PTB rate, OR 2.04). These findings suggest that a cutoff for excision depth of 15 mm or more could be applied to stratify patients with history of LLETZ-alone for increased antenatal surveillance and our results would support the use of this threshold (OR 1.88). We did not identify a correlation between depth of excision and delivery gestation in women with a history of LLETZ+PPTB with higher rates of PTB seen in all depth categories, this group is therefore at the highest-risk of recurrent PTB and should be seen in a PPC early in the second trimester irrespective of depth of excision.

5 | CONCLUSION

This study has identified that PPTB has a significantly greater impact on the subsequent risk of PTB compared with LLETZ, with women with a history of LLETZ-alone receiving antenatal care in a specialist PPC having a similar risk of preterm birth to a background obstetric population. Although a correlation with depth of excision and PTB was seen, the majority of deliveries were at 37 weeks or later, even for a depth of excision of 20 mm or more. Our results indicate that counseling regarding PTB risk should be individualized based on presence of risk factors, in particular previous obstetric history. Further research into the efficacy of prophylactic antenatal interventions in the prevention of PTB for post-excision populations is necessary and highly desirable.

CONFLICT OF INTEREST

ELM has served on advisory boards for Intuitive Surgical and Hope Against Cancer for unrelated work. The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

AC, TM, OB, PM, and ELM conceptualized the study. AC and TM collected the data. AC, OB, FD, PM, and ELM performed the data analysis and interpretation. AC drafted the article, AC, OB, FD, PM, and ELM critically revised it and AC, TM, OB, FD, PM, and ELM gave final approval of the version to be published.

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