Supplementary methods

1. Data cleaning

All study sites submitted pathology reports; 8 of the 13 study sites also submitted a study database. This meant that for most sites we had three sources from which data could be corroborated 1) pathology reports, 2) study site databases and 3) first and last dates of treatment submitted in phase I. Additionally a few inpatient treatments were identified through HES records. Although sites were required to submit information on ablative treatment, smoking status and ethnicity these fields were very scantly populated.

As part of the data cleaning process we identified three study sites where less than 30% of the first treatment dates provided in phase 2 matched those provided in phase 1. Data received by the coordinating centre was anonymised and therefore discrepancies had to be resolved by the study sites. Two out of the three of the study sites (Lancashire and Barts health) were able to identify where the problem had arisen, correct it and resubmit information from pathology reports for phase 2. One site (Wirral) was not able to do this and their data have been excluded from this analysis (see Figure 1). As a result of this situation (and constraints on time) information on ablative treatment, smoking and ethnicity collected for Lancashire and Barts was lost.

In all instances where the date of first colposcopy recorded in phase II did not match the date from phase I within one month, clarification from the study site was sought. As a result we excluded 63 births in women where queries were not resolved.

2. Definitions of high risk pregnancies

The following conditions (ICD10 diagnostic codes) were included in our definition of high risk pregnancy: Insulin-dependent diabetes mellitus (E10) or morbid/extreme obesity (E66.2 or E66.8) at any time; other forms of diabetes mellitus (E11-E14) or pregnancy care of habitual aborter (O26.2) if the diagnosis appears before the birth. Diabetes mellitus in pregnancy (O24), mental and behavioural disorders due to psychoactive substance use (F10-F19, excluding acute intoxication), mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the puerperium (O99.3), oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium (O10-O16, excluding O12), maternal care for (suspected) fetal abnormality and/or damage (O35), maternal care for hydrops fetalis (O36.2), maternal care for signs of fetal hypoxia (O36.3), Infection of amniotic sac and membranes (O41.1), premature separation of placenta [abruptio placentae] (O45), placenta praevia with haemorrhage (O44.1), supervision of high-risk pregnancy (Z35.8, Z35.9), presence of (intrauterine) contraceptive device (Z97.5), retained intrauterine contraceptive device in pregnancy (O26.3), hydrops fetalis due to haemolytic disease (P56), rupture of uterus before onset of labour (O71.0).

Overall 173 out of 2284 (7.6%) women in the study were dropped from the analysis. Because of the high risk of preterm birth in women with such conditions, the proportion of preterm birth among these women was very high: 129 out of 173 (74.6%) births were preterm. Details are provided in supplementary table 1.

3. Weights

Inverse probability of sampling (i.e. inclusion in phase II) weights were applied to the relative risk regression. Cases and controls were assigned different weights, to reflect the different proportions of cases and controls from Phase I that were selected for Phase II. Cases (preterm births) were assigned a weight of 1. The weights for the controls were calculated from:

$$\frac{\text{Number of cases in phase II/ Number of cases in phase I}}{\text{Number of controls in phase II/Number of controls in phase I}}$$

giving a weight of 9.54.

Supplementary Tables

Table A. High risk pregnancies: ICD codes and number of women with the code in the study

ICD10 Diagnostic Codes	Condition	Timing	Number of women
E10	Insulin-dependent diabetes mellitus	At any time	9
E66.2 or E66.8	Morbid/extreme obesity	At any time	1
E11-E14	Other forms of diabetes mellitus	Before the index birth	3
O26.2	Pregnancy care of habitual aborter	Before the index birth	2
O24	Diabetes mellitus in pregnancy	At the index birth	1
F10-F19, excl. acute intoxication	Mental and behavioural disorders due to psychoactive substance use	At the index birth	23
O99.3	Mental disorders and diseases of the nervous system complicating pregnancy, childbirth and the puerperium	At the index birth	43
O10-O16, excluding O12	Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium	At the index birth	25
O35	Maternal care for (suspected) fetal abnormality and/or damage	At the index birth	22
O36.2	maternal care for hydrops fetalis	At the index birth	1
O36.3	maternal care for signs of fetal hypoxia	At the index birth	15
O41.1	Infection of amniotic sac and membranes	At the index birth	0
O45	premature separation of placenta [abruptio placentae]	At the index birth	2
O44.1	Placenta praevia with haemorrhage	At the index birth	45
Z35.8, Z35.9	Supervision of high-risk pregnancy	At the index birth	11
Z97.5	Presence of (intrauterine) contraceptive device	At the index birth	0
O26.3	Retained intrauterine contraceptive device in pregnancy	At the index birth	0
P56	Hydrops fetalis due to haemolytic disease	At the index birth	1
O71.0	Rupture of uterus before onset of labour	At the index birth	1
Overall			173*

*Note: some women had more than one high risk ICD code

Table B. Relative risk of preterm birth by the depth (mm) of the excision in those treated by LLETZ and other excisional procedures.

	Cases		Controls		RR (95% CI)
	N	%	N	%	
Punch biopsy only	210	27.3	274	33.0	0.95 (0.72 to 1.26)
Small LLETZ (1-9mm deep)	168	21.9	215	25.9	1 (reference)
Medium LLETZ (10-14mm deep)	172	22.4	174	21.0	1.29 (0.97 to 1.70)
Large LLETZ (15-19mm deep)	69	9.0	41	4.9	2.01 (1.36 to 2.98)
Very large LLETZ (20+mm deep)	38	4.9	20	2.4	2.40 (1.43 to 4.05)
LLETZ with unknown treatment depth	61	7.9	68	8.2	1.15 (0.78 to 1.68)
Small/medium other excision (non-LLETZ)	15	2.0	20	2.4	0.95 (0.48 to 1.89)
Large/very large other excision (non-LLETZ)	27	3.5	15	1.8	2.18 (1.16 to 4.09)
Other excision (non-LLETZ) with unknown treatment depth	8	1.0	3	0.4	3.11 (1.03 to 9.40)
	768		830		

Table C. Relative risk of preterm birth by the depth (mm) in those with a piecemeal excisional treatment and those with one piece excised.

	Cases		Controls		RR (95% CI)
	N	%	N	%	
Punch biopsy only	210	27.3	274	33.0	1.00 (0.73 to 1.35)
Small (1-9mm deep), one piece	119	15.5	159	19.2	1 (reference)
Medium (10-14mm deep), one piece	128	16.7	140	16.9	1.24 (0.90 to 1.71)
Large (15-19mm deep), one piece	60	7.8	38	4.6	2.01 (1.30 to 3.12)
Very large (20+mm deep), one piece	39	5.1	22	2.7	2.25 (1.33 to 3.79)
Unknown treatment depth, one piece	56	7.3	52	6.3	1.38 (0.91 to 2.10)
Small/medium (1-14mm deep), piecemeal	108	14.1	110	13.3	1.32 (0.93 to 1.85)
Large/very large (15+mm deep), piecemeal	35	4.6	16	1.9	2.69 (1.54 to 4.70)
Unknown treatment depth, piecemeal	13	1.7	19	2.3	1.01 (0.49 to 2.07)

Table D. Adjusted relative risk (RR)[1] of preterm birth comparing the depth of the excisional treatment with the volume of tissue excised in those attending colposcopy before birth

			Depth				
			Small (<10mm)	Medium(10-14mm)	Large (15-19mm)	Very large (≥20mm)	Unknown
Volume	Small ≤1.77cm3	N **RR (95% CI)** *absolute risk*	334 **1 (reference)** *7.5%*	160 **1.02 (0.70 to 1.47)** *7.6%*	29 **1.50 (0.71 to 3.17)** *11.2%*	3 **3.08 (0.37 to 25.87)** *23.0%*	
	Medium 1.78-2.65cm3	N **RR (95% CI)** *absolute risk*	36 **1.11 (0.57 to 2.15)** *8.3%*	118 **1.40 (0.93 to 2.12)** *10.4%*	22 **4.08 (1.79 to 9.28)** *30.4%*	9 **0.63 (0.16 to 2.53)** *4.7%*	
	Large >2.65cm3	N **RR (95% CI)** *absolute risk*	26 **1.37 (0.65 to 2.90)** *10.2%*	90 **2.16 (1.38 to 3.36)** *16.1%*	77 **1.99 (1.24 to 3.18)** *14.8%*	70 **3.02 (1.80 to 5.06)** *22.5%*	
	Unknown	N **RR (95% CI)** *absolute risk*					140 **1.32 (0.90 to 1.93)** *9.8%*

[1]Relative risks (RR) are adjusted by parity, index of multiple deprivation, maternal age at delivery and study site