Review

Loop Electrosurgical Excision Procedure and Risk of Preterm Birth

A Systematic Review and Meta-analysis

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OBJECTIVE: To assess whether loop electrosurgical excision procedure (LEEP) increases the risk for preterm birth before 37 weeks of gestation and clarify whether the increased risk for preterm birth is attributable to the procedure itself or to risk factors associated with cervical dysplasia.

DATA SOURCES: Two authors performed a search of the relevant data through February 2013 using PubMed, Embase, Scopus, CENTRAL, and ClinicalTrials.gov.

METHODS OF STUDY SELECTION: We included observational studies that compared rates of preterm birth in women with prior LEEP with women with no history of cervical excision. Nineteen of 559 identified studies met selection criteria.

TABULATION, INTEGRATION, AND RESULTS: We compared women with a history of LEEP with two unexposed groups without a history of cervical excision: 1) women with an unknown or no history of cervical dysplasia; and 2) women with a history of cervical dysplasia but no cervical excision. The primary outcome was preterm birth before 37 weeks of gestation. Secondary outcomes were preterm birth before 34 weeks of gestation, spontaneous preterm birth, preterm premature rupture of membranes, and perinatal mortality. DerSimonian-Laird random effects models were used. We assessed heterogeneity between studies using the Q and I^2 tests. Stratified analyses and metaregression were performed to assess confounding. Nineteen studies were included with a total of 6,589 patients with a history of LEEP and 1,415,015 without. Overall, LEEP was associated with an increased risk of preterm birth before 37 weeks of gestation (pooled relative risk 1.61, 95% confidence interval [CI] 1.35–1.92). However, no increased risk was found when women with a history of LEEP were compared with women with a history cervical dysplasia but no cervical excision (pooled relative risk 1.08, 95% CI 0.88–1.33).

CONCLUSION: Women with a history of LEEP have similar risk of preterm birth when compared with women with prior dysplasia but no cervical excision. Common risk factors for both preterm birth and dysplasia likely explain findings of association between LEEP and preterm birth, but LEEP itself may not be an independent risk factor for preterm birth.

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In the United States, approximately 12% of all neonates are born preterm.[1] Preterm birth is a leading cause of neonatal morbidity and mortality. Prior cervical procedures, particularly excisional procedures used to diagnose and treat cervical dysplasia, are a commonly cited risk factor for preterm delivery.[2] This is important because in the United States alone, more than 400,000 women are diagnosed with cervical dysplasia annually and the majority are among women of childbearing age.[3]

Many prior studies have investigated the risk of preterm birth in women who have had one of the three primary methods of cervical excision, namely cold knife conization, laser cone, or loop electrosurgical excision procedure (LEEP). These studies have yielded conflicting results as to the risk of preterm

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birth after cervical excisional procedures. A possible explanation is that they have used differing unexposed groups, have varying inclusion and exclusion criteria, and do not uniformly control for confounding factors. Meta-analysis has been used in the past to attempt to explore the variability of results and pool the available data.[4–7] However, after the most recent meta-analysis, several well-performed studies have been published.[7] Additionally, the most recent systematic reviews and meta-analyses combined results from all cervical excisional procedures rather than focusing on LEEP, the most commonly performed type of procedure. This approach limits the application of the results to contemporary gynecologic practice.

An important consideration in estimating the risk of preterm birth after LEEP is whether the increased risk for preterm birth is attributable to the cervical excision procedure itself or secondary to risk factors associated with cervical dysplasia. Establishing whether LEEP is a true risk factor for preterm birth is imperative to assist health care practitioners in counseling patients who present with dysplasia and in making optimal treatment decisions.

SOURCES

We performed a systematic review and meta-analysis based on a predesigned protocol. The protocol outlined the research question, populations, exposures, outcomes of interest, search strategies, study selection, exclusion criteria, methods of data abstraction, and statistical analysis. All methods followed the guidelines set forth by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.[8]

Two authors (S.N.C. and H.A.F.) and a medical librarian trained in systematic reviews conducted a search of the existing literature through February 2013. We searched the databases using standard term indices to cover the concepts of "cervical dysplasia," "preterm birth," and "cervical excision." The search model was created based on guidelines published in the *Cochrane Handbook for Systematic Review of Interventions*.[9] We searched the databases PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. Duplicate studies were removed and two of the authors (S.N.C. and H.A.F.) screened the remaining publications for relevance and fulfillment of predefined inclusion and exclusion criteria. We identified additional publications by hand-searching citation lists of the retrieved articles.

STUDY SELECTION

We included cohort and case–control studies that compared rates of preterm birth in women with prior LEEP with women who had no history of cervical excision. We excluded studies that compared preterm birth rates in the same group of women before and after LEEP and those without a defined comparison group. Because LEEP is the most commonly performed procedure for cervical dysplasia,[10,11] and the focus of our study, we excluded studies that reported only preterm birth rates after other types of cervical excisional procedures such as cold knife conization or laser conization and nonexcisional therapies for cervical dysplasia. In addition, we excluded studies that combined women who had a prior LEEP with women with other types of excision as a single exposure group and did not report rates of preterm birth among women with prior LEEP separately. We also excluded case series, case reports, abstracts, unpublished data, expert opinions, studies that studied LEEP only in women who were pregnant at the time of the procedure, studies that included women who had a LEEP for invasive cancer, and non-English publications. When multiple studies examined the same cohort of women, we included the study that provided the most data on our primary and secondary outcomes.

Two authors (S.N.C. and H.A.F.) independently evaluated each study. Data abstracted included description of the unexposed group(s), identification of possible sources of bias that could affect the quality of the study, and rates of the outcomes.

The primary outcome was preterm birth before 37 weeks of gestation. Secondary outcome measures were preterm birth before 34 weeks of gestation, spontaneous preterm birth, preterm premature rupture of membranes, and perinatal mortality.

The exposure was a history of LEEP for treatment of cervical dysplasia. Two categories of unexposed were identified: 1) women with no or unknown history of cervical dysplasia; and 2) women with a history of cervical dysplasia but no cervical excisional procedure.

Differences in design, analysis, and reporting among studies can be sources of significant statistical bias in meta-analyses.[9,12] Rather than using quality scoring systems, which may be poorly discriminatory, we assessed study quality based on three factors we considered most likely to threaten study validity: 1) selection bias; 2) independence of outcome measures; and 3) data source quality. Risk of selection bias in each study was judged to be high or low based on the methods used to identify exposed and unexposed women. Independence of outcomes measures was defined by the pregnancy that was evaluated in the exposure group. Outcomes were considered independent if only the first pregnancy or first pregnancy greater than 20 weeks after LEEP was included in analysis. Lastly, we classified data source quality as high if the study was prospective or used a database or registry that was validated or reported minimal missing data, whereas medical records, databases or registries of uncertain quality, and surveys were considered lower quality. Overall quality was assessed as higher if at least two of the three criteria were assessed as favorable.

Data were analyzed using Stata 12.0 with METAN software package. Raw data were abstracted from each study and combined using the DerSimonian-Laird random-effects model, which accounts for between- and within-study variance. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated for the primary and secondary outcomes if more than two studies reported the specific outcome. All outcomes evaluated were categorical. If a study included more than one unexposed group, the raw data were combined so that an overall rate of the outcomes was considered for analysis. Results were plotted graphically as forest plots.

We assessed statistical heterogeneity using Cochran's Q (qualitative) and Higgins I^2 (quantitative) tests.[13] To take into account the low statistical power of tests of heterogeneity, we considered statistically significant heterogeneity as Cochran's Q test with a $P<.1$ or I^2 greater than 30%. Sources of heterogeneity were further explored by stratifying on individual variables. We also performed metaregression to estimate how much of the heterogeneity was explained by covariates. We assessed publication bias graphically using funnel plots and statistically using the Harbord test.[14] The Harbord test is a parametric test to estimate whether there is significant correlation between effects size and sample size, which supports the presence of publication bias.

RESULTS

The flow diagram of study identification for the meta-analysis is illustrated in Figure 1. A total of 559 potentially relevant publications was identified. After exclusion of duplications and studies not relevant to the topic of interest, 47 studies remained and were retrieved for detailed review. Studies were further eliminated for the following indications: meta-analyses, inclusion of cases of invasive cancer, use of an inappropriate unexposed group, no outcome of preterm birth before 37 weeks of gestation, and reporting data only after exposure to other forms of excision (laser or cold knife cone). Ultimately, 19 publications remained after excluding duplicated cohorts and studies that evaluated multiple types of excision because the exposure and LEEP data could not be extracted independently.[15–33] Of the 19 included studies, 16 were retrospective cohort, two were prospective cohort, and one was a case–control study. In total, the studies included 6,589 patients with a history of LEEP (exposed), and 1,415,015 without a history of LEEP (unexposed). Table 1 details the characteristics of the included studies, providing each study's year of publication, country, study design, inclusion and exclusion criteria,

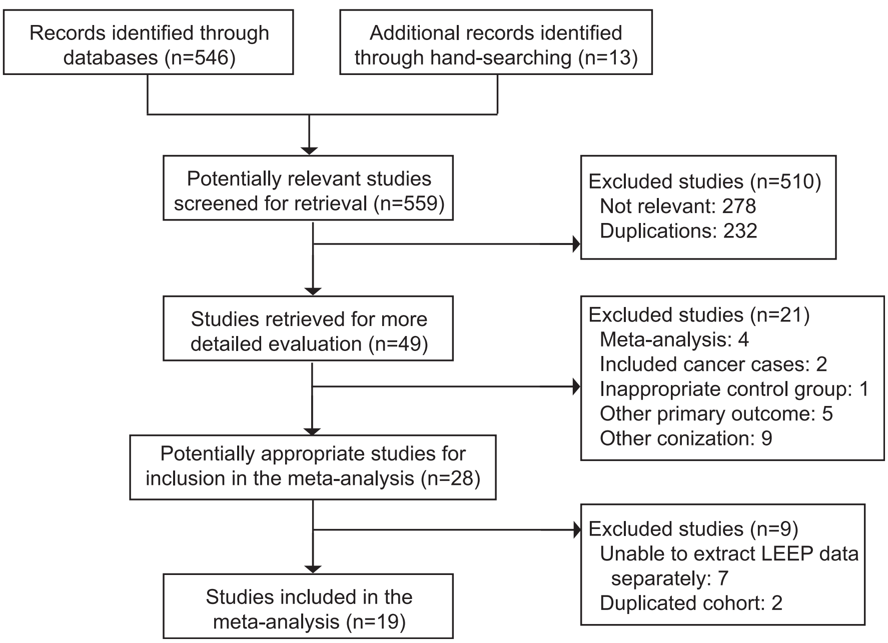

Fig. 1. Flow diagram of studies in meta-analysis. LEEP, loop electrosurgical excision procedure.

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Table 1. Characteristics of Included Studies

Study	Year	Country	Study Design	Inclusion Criteria	Exclusion Criteria	LEEP (n)	Unexposed
Haffenden	1993	U.K.	Retrospective cohort	Pregnancy post-LEEP	Birth less than 24 wk of gestation	152	Unknown dysplasia history, no prior treatment, N=152
Blomfield	1993	U.K.	Retrospective cohort	Pregnancy post-LEEP	Birth less than 20 wk of gestation	40	Unknown dysplasia history, no prior treatment, N=80
Braet	1994	U.K.	Retrospective cohort	First pregnancy post-LEEP	Multiple gestation	78	Unknown dysplasia history, no prior treatment, N=78
Cruickshank	1995	U.K.	Retrospective cohort	First pregnancy post-LEEP	Birth less than 20 wk of gestation, multiple gestation	149	Unknown dysplasia history, no prior treatment, N=298
Sadler	2004	New Zealand	Retrospective cohort	First pregnancy post-LEEP	Birth less than 20 wk of gestation, multiple gestation, LEEP during pregnancy	278	Prior dysplasia, no prior treatment, N=426
Tan	2004	U.K.	Retrospective cohort	First pregnancy post-LEEP	Age older than 35 y	119	Unknown dysplasia history, no prior treatment, N=119
Acharya	2005	Norway	Retrospective cohort	First pregnancy post-LEEP	Age older than 45 y, birth less than 20 wk of gestation	79	Unknown dysplasia history, no prior treatment, N=158
Samson	2005	Canada	Retrospective cohort	First pregnancy post-LEEP	Birth less than 20 wk of gestation, multiple gestation, prior preterm birth, indicated deliveries	571	Unknown dysplasia history, no prior treatment, N=571
Crane	2006	Canada	Prospective cohort	Pregnancy post-LEEP	Multiple gestation	75	Unknown dysplasia history, no prior treatment, N=144
Nohr	2007	Denmark	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation, indicated deliveries, stillbirth	349	Unknown dysplasia history, no prior treatment, N=14,567
Himes	2007	U.S.	Retrospective cohort	First pregnancy post-LEEP	Birth less than 20 wk of gestation, multiple gestation, anomalies, LEEP during pregnancy	114	Prior dysplasia, no prior treatment, N=962
Jakobsson	2007	Finland	Retrospective cohort	Pregnancy post-LEEP	Age older than 49 y, age younger than 15 y, multiple gestation	2,690	Unknown dysplasia history, no prior treatment, N=1,056,855
Ortoft	2010	Denmark	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation, indicated deliveries	572	No history of dysplasia or prior treatment, N=72,899
Werner	2010	U.S.	Retrospective cohort	First pregnancy post-LEEP	Multiple gestation, LEEP during pregnancy	511	Unknown dysplasia history, no prior treatment, N=240,348 Prior dysplasia, no prior treatment, N=842

(*continued*)

Table 1. Characteristics of Included Studies (*continued*)

Study	Year	Country	Study Design	Inclusion Criteria	Exclusion Criteria	LEEP (n)	Unexposed
Andia	2011	Spain	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation	189	Unknown dysplasia history, no prior treatment, N=189 Prior dysplasia, no prior treatment, N=189
Lima	2011	Portugal	Retrospective cohort	Pregnancy post-LEEP	None	18	Unknown dysplasia history, no prior treatment, N=58
Poon	2012	U.K.	Case–control	Pregnancy post-LEEP	Multiple gestation, cerclage, anomalies, preterm PROM, contractions, progesterone, indicated deliveries	473	Unknown dysplasia history, no prior treatment, N=25,772
Van Hentenryck	2012	Belgium	Retrospective cohort	Pregnancy post-LEEP	None	40	Unknown dysplasia history, no prior treatment, N=212
Simoens	2012	Belgium	Prospective cohort	Pregnancy post-LEEP	Birth less than 20 wk, multiple gestation	52	No history of dysplasia or prior treatment, N=104

LEEP, loop electrical excision procedure; U.K., United Kingdom; PROM, premature rupture of membranes.

unexposed group used, and number of participants in the LEEP and unexposed groups.

The results of the methodologic quality assessment of each study are shown in Table 2. Based on evaluations in three categories, seven studies were classified as higher quality and 12 as lower quality. The higher quality studies all had low risk of selection bias, and most had independence of outcome measures. Conversely, of the studies categorized as lower quality, almost all had high risk of selection bias and lower quality of their data source.

Table 3 shows the rates in the exposed and unexposed groups, pooled RR, 95% CI, and measures of heterogeneity for our primary outcome of preterm birth before 37 weeks of gestation, results of stratified analyses, and secondary outcomes. Consistent with our inclusion criteria for the meta-analysis, all studies reported preterm birth before 37 weeks of gestation as an outcome. Overall, LEEP was associated with a higher risk of preterm birth before 37 weeks of gestation (19 studies: 8.8% compared with 5.1%, pooled RR 1.61, 95% CI 1.35–1.92; Fig. 2). There was evidence of statistical heterogeneity among studies (P=.001, I^2=59.2%). Sources of heterogeneity were explored using stratified analyses to evaluate the effect of the comparison group used and study quality. There was no statistically significant difference in the risk of preterm birth when the prior LEEP group was compared with unexposed women with a history of cervical dysplasia but no cervical excision (four studies: 10.0% compared with 7.2%, pooled RR 1.08, 95% CI 0.88–1.33; Fig. 3). On the other hand, the association between LEEP and preterm birth persisted when the comparison group was women with either no history or unknown history of dysplasia (15 studies: 8.6% compared with 4.6%, pooled RR 1.86, 95% CI 1.58–2.21). In addition, when stratifying by study quality, the association between LEEP and preterm birth was lower for higher quality studies (seven studies: 8.4% compared with 5.1%, pooled RR 1.48, 95% CI 1.14–1.91) compared with lower quality studies (12 studies: 10.0% compared with 4.1%, pooled RR 1.75, 95% CI 1.36–2.26) (Fig. 4). Using metaregression, comparison group type and study quality accounted for 83.8% of the heterogeneity between studies, leaving a nonsignificant residual heterogeneity of 28.9% (I^2res=28.9%, adjusted R^2=83.8%). Importantly, there was no evidence of publication bias (Harbord's P=.96) (Fig. 5).

We were able to isolate the secondary outcome of spontaneous preterm birth before 37 weeks of gestation in eight studies. There was significant heterogeneity between studies (P<.001, I^2=73.6%). Notably, we

Table 2. Quality Assessment of Included Studies

Study	Year	Selection Bias Risk	Independence of Outcome Measures	Data Source Quality	Overall Study Quality
Haffenden	1993	High	Unknown	Low	Lower
Blomfield	1993	High	Unknown	Low	Lower
Braet	1994	High	Yes	Low	Lower
Cruickshank	1995	High	Yes	Low	Lower
Sadler	2004	Low	Yes	High	Higher
Tan	2004	High	Yes	Low	Lower
Acharya	2005	Low	Yes	Low	Higher
Samson	2005	Low	Yes	High	Higher
Crane	2006	High	No	High	Lower
Nohr	2007	High	No	Low	Lower
Himes	2007	Low	Yes	Low	Higher
Jakobsson	2007	Low	No	High	Higher
Ortoft	2010	Low	Unknown	Low	Lower
Werner	2010	Low	Yes	Low	Higher
Andia	2011	High	Unknown	Low	Lower
Lima	2011	High	Unknown	Low	Lower
Poon	2012	Low	Unknown	High	Higher
Van Hentenryck	2012	High	No	Low	Lower
Simoens	2012	High	No	Low	Lower

found a similar magnitude of increase in the risk of spontaneous preterm birth before 37 weeks of gestation, although no longer statistically significant (eight studies: 6.8% compared with 3.4%, pooled RR 1.60, 95% CI 0.99–2.55). Meta-analysis of studies that reported on the outcome of preterm premature rupture of membranes, revealed a more than twofold increased risk for preterm premature rupture of membranes among women with a history of LEEP (six studies: 5.1% compared with 2.5%, pooled RR 2.37, 95% CI 1.64–3.44). Women with a history of LEEP were also found to have a significantly increased risk for preterm birth before 34 weeks of gestation (five studies: 2.9% compared with 2.3%, pooled RR 2.21, 95% CI 1.33–3.67) in studies that reported that outcome. Finally, the risk of perinatal mortality was elevated in women with a history of LEEP but not statistically significant (1.0% compared with 0.8%, pooled RR 1.63, 95% CI 0.95–2.80).

Table 3. Rates and Pooled Estimates for Primary Outcome, Stratified Analyses, and Secondary Analyses

Outcome	No. of Studies	Exposed % (n Outcome/n Exposed)	Unexposed % (n Outcome/n Unexposed)	Pooled RR	95% CI	Heterogeneity: Cochran's *P*	Heterogeneity: I^2 (%)
Preterm birth less than 37 wk of gestation	19	8.8 (582/6,549)	5.1 (71,732/1,415,023)	1.61	1.35–1.92	.001	59.2
Stratified by study unexposed group							
No or unknown history of dysplasia	15	8.6 (473/5,457)	4.6 (54,036/1,172,059)	1.86	1.58–2.21	.069	37.7
History of dysplasia	4	10.0 (109/1,092)	7.2 (17,696/242,946)	1.08	0.88–1.33	.654	0.00
Stratified by study quality							
Lower	12	10.3 (188/1,833)	4.1 (3,627/89,089)	1.75	1.36–2.26	.057	42.8
Higher	7	8.4 (394/4,716)	5.1 (68,105/1,325,926)	1.48	1.14–1.91	.001	72.1
Spontaneous preterm birth less than 37 wk of gestation	8	6.8 (147/2,175)	3.4 (11,684/342,097)	1.60	0.99–2.55	<.001	73.6
Preterm PROM	6	5.1 (108/2,102)	2.5 (7,940/314,891)	2.37	1.64–3.44	.094	46.9
Preterm birth less than 34 wk of gestation	5	2.9 (48/1,670)	2.3 (6,053/267,889)	2.21	1.33–3.67	.157	39.6
Perinatal mortality	7	1.0 (19/1,925)	0.8 (2,496/315,118)	1.63	0.95–2.80	.911	0.00

RR, relative risk; CI, confidence interval; PROM, premature rupture of membranes.

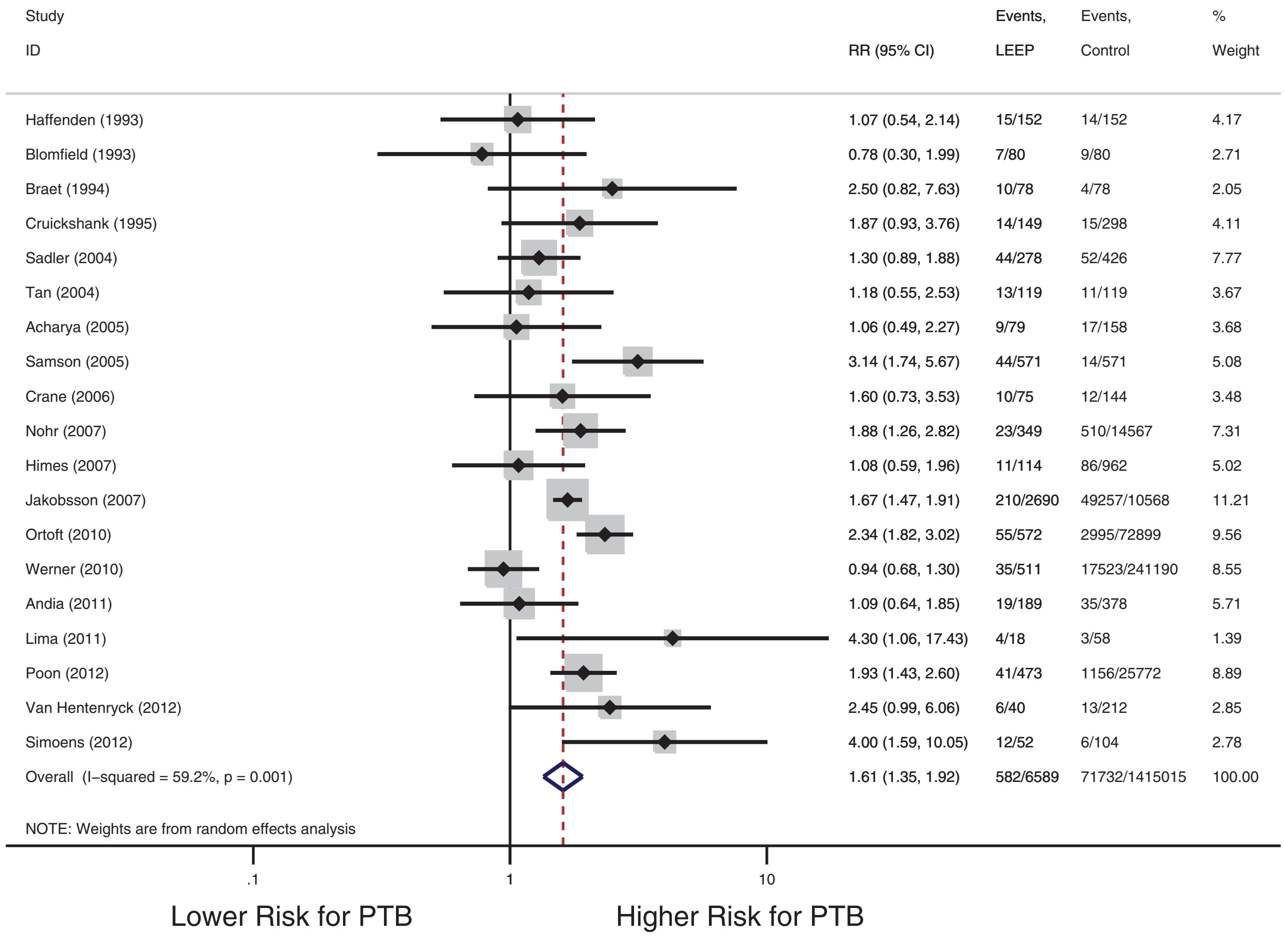

Fig. 2. Forest plot loop electrosurgical excision and preterm birth at less than 37 weeks of gestation. RR, relative risk; CI, confidence interval; LEEP, loop electrosurgical excision procedure; PTB, preterm birth.
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CONCLUSION

We found that whereas women with a history of LEEP are at increased risk for preterm birth before 37 weeks of gestation, the risk was not significantly different when compared with women with prior dysplasia but no cervical excision. This suggests that the risk factors for dysplasia and preterm birth are shared and that LEEP by itself may not be an independent risk factor for preterm birth.

Although multiple prior meta-analyses have been performed investigating the risk of preterm birth in women with a history of a cervical excision procedure for dysplasia, our study offers several improvements over previous meta-analyses on the subject.[4–7] We included six new studies that have been published since the most recent meta-analysis. Notably, our analysis examined two types of comparison groups, enabling us to estimate whether LEEP itself or shared risk factors between cervical dysplasia and preterm birth explain the increased risk of preterm birth in women with a history of LEEP. The ability to stratify by multiple factors and perform metaregression allowed us to account for heterogeneity between studies. Another strength of our study was our extensive search of the literature by two reviewers, including five databases, with the aid of a Master of Library and Information Science–credentialed librarian, yielding a transparent and reproducible search strategy. In addition, by focusing solely on LEEP, instead of cervical excision procedures as a whole, we give an accurate risk assessment that can be applied to the most commonly used cervical excision procedure in contemporary practice. Lastly, our study differs from the most recent meta-analysis in providing risk estimates for multiple secondary outcomes, including spontaneous preterm birth.

Despite the strengths, the potential limitations of our study must be considered as well. Although an

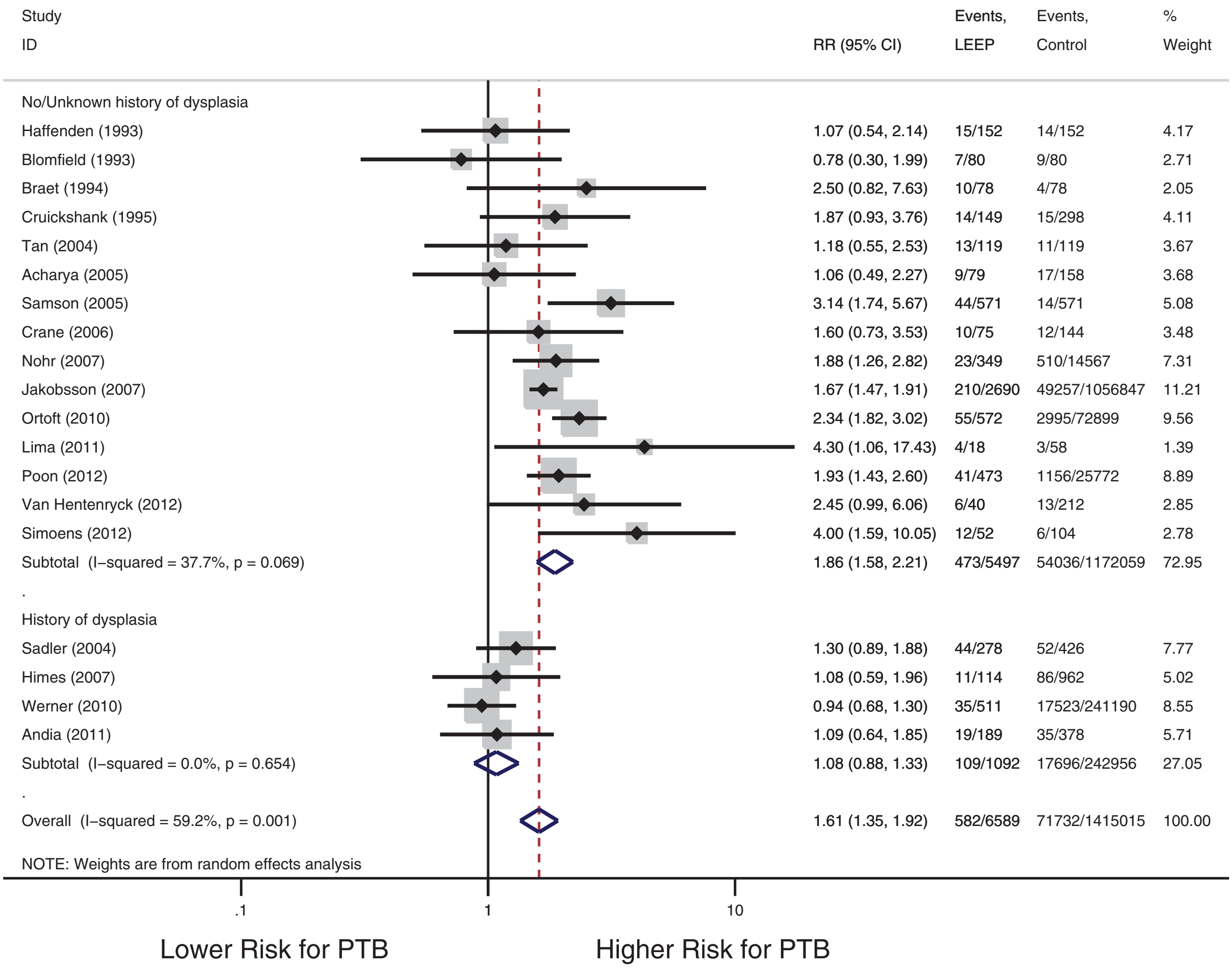

Fig. 3. Forest plot loop electrosurgical excision and preterm birth stratified by unexposed group. RR, relative risk; CI, confidence interval; LEEP, loop electrosurgical excision procedure; PTB, preterm birth.

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extensive search strategy was used, the exclusion of non-English studies could have introduced possible selection bias. To meet our inclusion criteria of LEEP only, we excluded studies in which we were unable to extract LEEP data separately. By excluding these studies, some data on LEEP and subsequent preterm birth were lost. In addition, like all meta-analyses, the quality of our findings is dependent on the quality of the primary studies included. It must be considered that many of the included studies were from countries in which the preterm birth rate is low compared with the United States. Therefore, the results may be different in countries with higher preterm birth rates. On the other hand, inclusion of studies from diverse countries increases the generalizability of our findings. Additionally, as a result of the smaller number of studies from which the secondary outcomes were drawn, it was not possible to stratify by different unexposed groups as performed for the primary outcome. Another consideration is that the unexposed groups were combined in the stratified analysis for Andia et al and Werner et al. Therefore, some women with an unknown history of dysplasia were included with women with history of dysplasia. However, combining these unexposed groups would serve to bias our results away from the null of no difference. This direction of any potential bias lends credence to the finding of no difference in the risk of preterm birth observed. Finally, it may be argued that the lack of significant difference in the risk of preterm birth when women with a history of LEEP are compared with those with a history of cervical dysplasia, but no excision, is the result of lower statistical power. On the contrary, post hoc power analysis showed that the

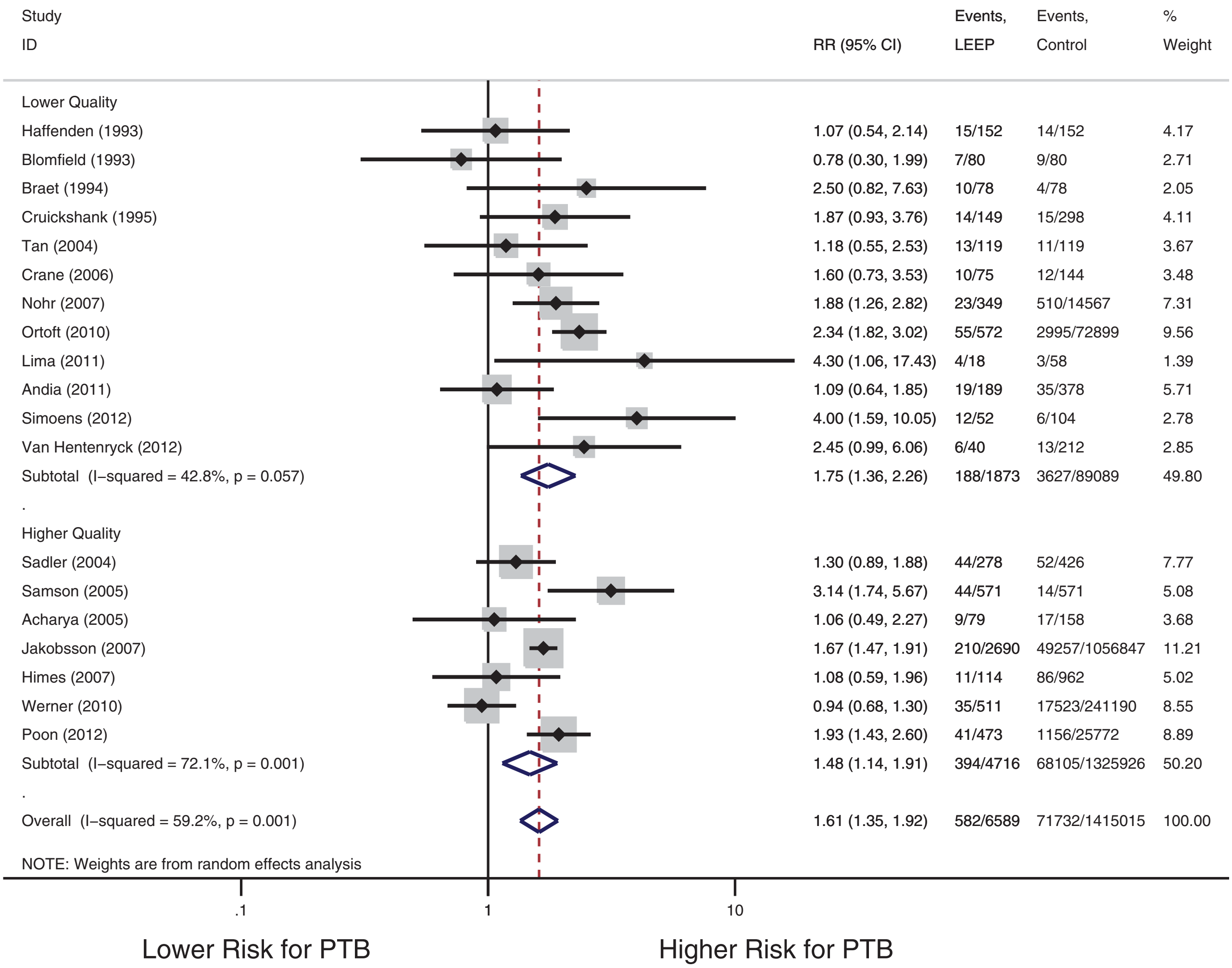

Fig. 4. Forest plot loop electrosurgical excision and preterm birth stratified by study quality. RR, relative risk; CI, confidence interval; LEEP, loop electrosurgical excision procedure; PTB, preterm birth.
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1,092 exposed and 242,966 unexposed women provide greater than 99% power to detect the 61% increased risk of preterm birth suggested by the overall pooled analysis.

In conclusion, results of this systematic review and meta-analysis of the current body of literature suggest that the notion that LEEP increases the risk of preterm birth needs to be reevaluated. Our results indicate that the increased risk for preterm birth before 37 weeks of gestation in women with a history of LEEP may be related to shared risk factors rather than the cervical excision procedure itself. Larger studies with carefully selected comparison groups that are similar to women with a history of LEEP would further clarify the relationship between LEEP and preterm birth. Additionally, patient-level data could be used in a future review for a detailed investigation

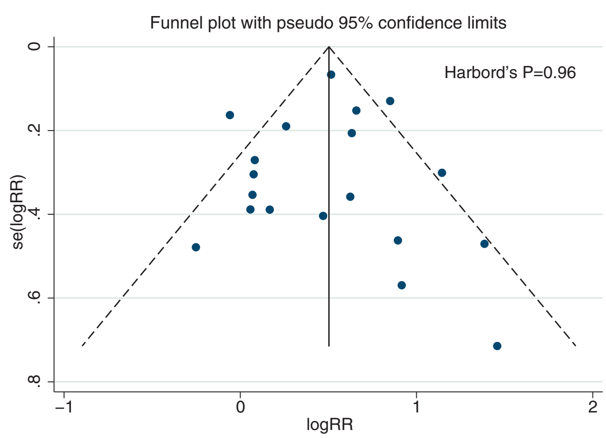

Fig. 5. Funnel plot and publication bias.
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into individual risk factors for dysplasia and preterm birth. Currently, health care practitioners are urged to weigh the potential benefits of treating dysplasia with LEEP compared with the risk to future pregnancies.[2] If our finding that LEEP is not an independent risk factor for preterm birth is confirmed, the risk and benefit discussion with patients regarding the option of LEEP or expectant management would be altered, thus ensuring optimal therapy without fear of increasing the risk of preterm birth.

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