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Loop Electrosurgical Excision Procedure and Risk of Preterm Birth: A Systematic Review and Meta-analysis

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Abstract

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 utilizing 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 to women with no history of cervical excision. Nineteen out of 559 identified studies met selection criteria.

Tabulation, Integration, and Results—We compared women with a history of LEEP to two unexposed groups without a history of cervical excision: 1) women with unknown or no history of cervical dysplasia; and 2) women with history of cervical dysplasia, but no cervical excision. The primary outcome was preterm birth before 37 weeks. Secondary outcomes were preterm birth before 34 weeks, 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 meta-regression were performed to assess confounding. Nineteen studies were included, with a total of 6,589 patients with history of LEEP, and 1,415,015 without. Overall, LEEP was associated with an increased risk of preterm birth before 37 weeks (pooled RR 1.61, 95% CI 1.35–1.92). However, no increased risk was found when women with a history of LEEP were compared to women with a history cervical dysplasia but no cervical excision (pooled RR 1.08, 95% CI 0.88–1.33).

Conclusion—Women with history of LEEP have similar risk of preterm birth when compared to 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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INTRODUCTION

In the United States, approximately 12% of all infants 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 US alone, over 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 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 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.C. and H.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, CENTRAL (Cochrane Central Register of Controlled Trials), and ClinicalTrials.gov. Duplicate studies were removed and two of the authors (S.C. and H.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.

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STUDY SELECTION

We included cohort and case-control studies that compared rates of preterm birth in women with prior LEEP to 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 following other types of cervical excisional procedures, such as cold knife conization or laser conization, and non-excisional 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.C. and H.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 prior to 37 weeks of gestation. Secondary outcome measures were preterm birth before 34 weeks of gestation, spontaneous preterm birth , preterm premature rupture of membranes (PROM), 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 3 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 >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, while 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 was analyzed using Stata 12.0 with METAN software package (Stata-Corp, College Station, TX). Raw data was abstracted from each study and combined using the DerSimonian-Laird random-effects model which accounts for between and within study

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variance. Pooled relative risks (RR) with 95% confidence intervals 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 $p<0.1$ or $I^2 >30\%$. Sources of heterogeneity were further explored by stratifying on individual variables. We also performed meta-regression 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 were 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, and reporting data only after exposure to other forms of excision (laser or cold knife cone). Ultimately, nineteen publications remained after excluding duplicated cohorts and studies that evaluated multiple types of excision as the exposure and LEEP data could not be extracted independently. (15–33) Of the nineteen included studies, 16 were retrospective cohort, 2 were prospective cohort, and 1 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, unexposed group used, and number of subjects in the LEEP and unexposed groups.

The results of the methodological quality assessment of each study are shown in Table 2. Based on evaluations in three categories, seven studies were classified as higher quality and twelve 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, 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 (19

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studies: 8.8% vs. 5.1%, pooled RR 1.61, 95% CI 1.35–1.92; Figure 2). There was evidence of statistical heterogeneity among studies (P=0.001, 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 to unexposed women with a history cervical dysplasia but no cervical excision (4 studies: 10.0% vs. 7.2%, pooled RR 1.08, 95% CI 0.88–1.33; Figure 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% vs. 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 (7 studies: 8.4% vs. 5.1%, pooled RR 1.48, 95% CI 1.14–1.91) compared to lower quality studies (12 studies: 10.0% vs. 4.1%, pooled RR 1.75, 95% CI 1.36–2.26). Using meta-regression, comparison group type and study quality accounted for 83.8% of the heterogeneity between studies, leaving a non-significant residual heterogeneity of 28.9% (I^2res= 28.9%, Adj R^2 =83.8%). Importantly, there was no evidence of publication bias (Harbord's P=0.96) (Figure 4).

We were able to isolate the secondary outcome of *spontaneous* preterm birth before 37 weeks in eight studies. There was significant heterogeneity between studies (P<0.001, I^2= 73.6%). Notably, we found a similar magnitude of increase in the risk of spontaneous preterm birth before 37 weeks, although no longer statistically significant (8 studies: 6.8% vs. 3.4%, pooled RR 1.60, 95% CI 0.99–2.55). Meta-analysis of studies that reported on the outcome of preterm PROM, revealed an over 2-fold increased risk for preterm PROM amongst women with a history of LEEP (6 studies: 5.1 % vs. 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 (5 studies: 2.9% vs. 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 history of LEEP, but not statistically significant (1.0% vs. 0.8%, pooled RR 1.63, 95% CI 0.95–2.80).

CONCLUSION

We found that whereas women with a history of LEEP are at increased risk for preterm birth before 37 weeks, the risk was not significantly different when compared to 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.

While 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 6 new studies that have been published since the most recent meta-analysis. Notably, our analysis examined 2 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 meta-regression allowed us to account for heterogeneity between studies.

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Another strength of our study was our extensive search of the literature by 2 reviewers, including 5 databases, with the aid of a Master of Library and Information Science (MLIS) 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 extensive search strategy was employed, the exclusion of non-English studies could have introduced possible selection bias. In order to meet our inclusion criteria of LEEP only, we excluded studies where we were unable to extract LEEP data separately. By excluding these studies, some data on LEEP and subsequent preterm birth was 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 to 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, due to 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 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 to those with a history of cervical dysplasia, but no excision, is due to lower statistical power. On the contrary, post hoc power analysis showed that the 1092 exposed and 242, 966 unexposed women provide >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 re-evaluated. Our results indicate that the increased risk for preterm birth before 37 weeks 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 utilized in a future review for a detailed investigation into individual risk factors for dysplasia and preterm birth. Currently, practitioners are urged to weigh the potential benefits of treating dysplasia with LEEP versus 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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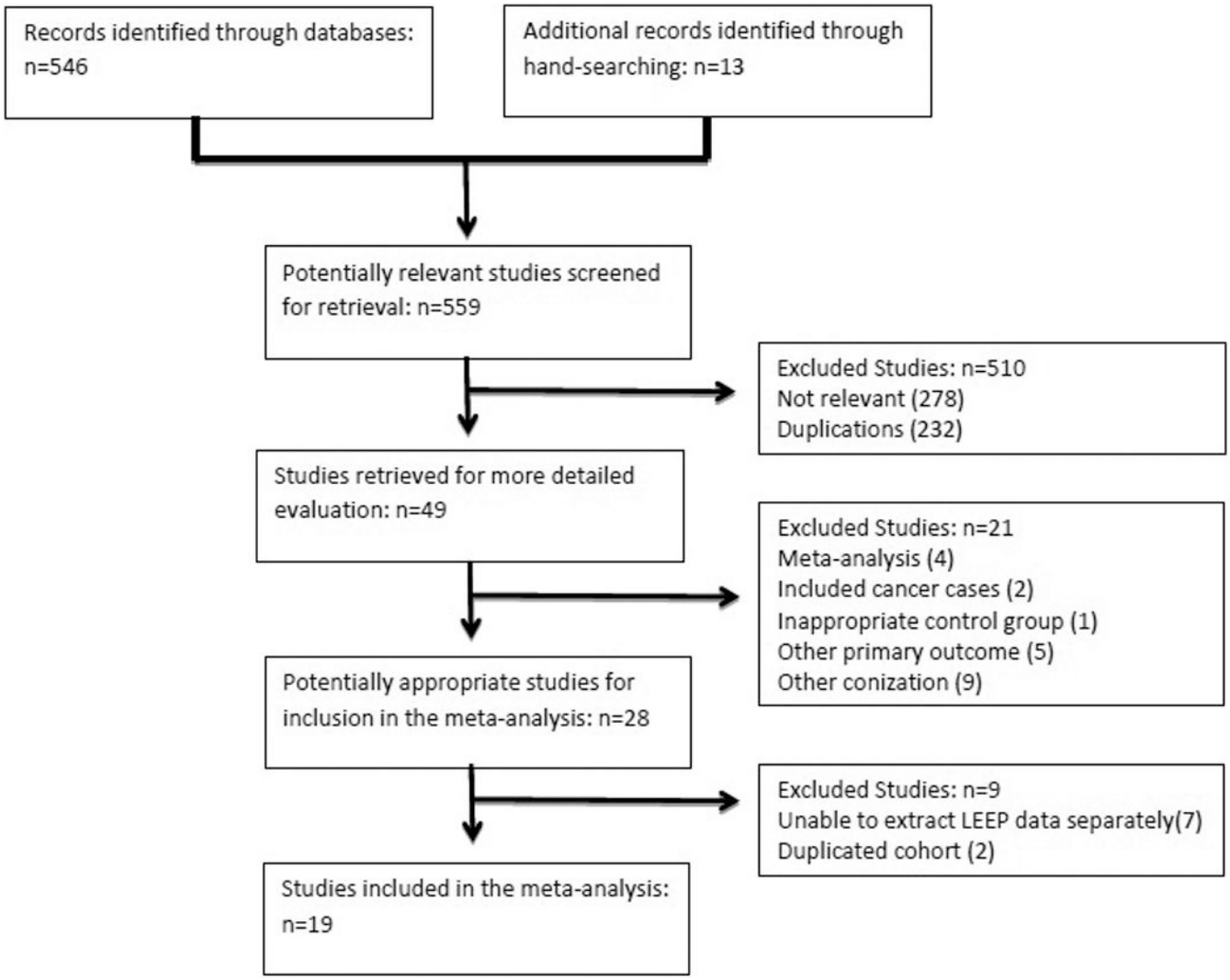

Figure 1.
Flow diagram of studies in meta-analysis

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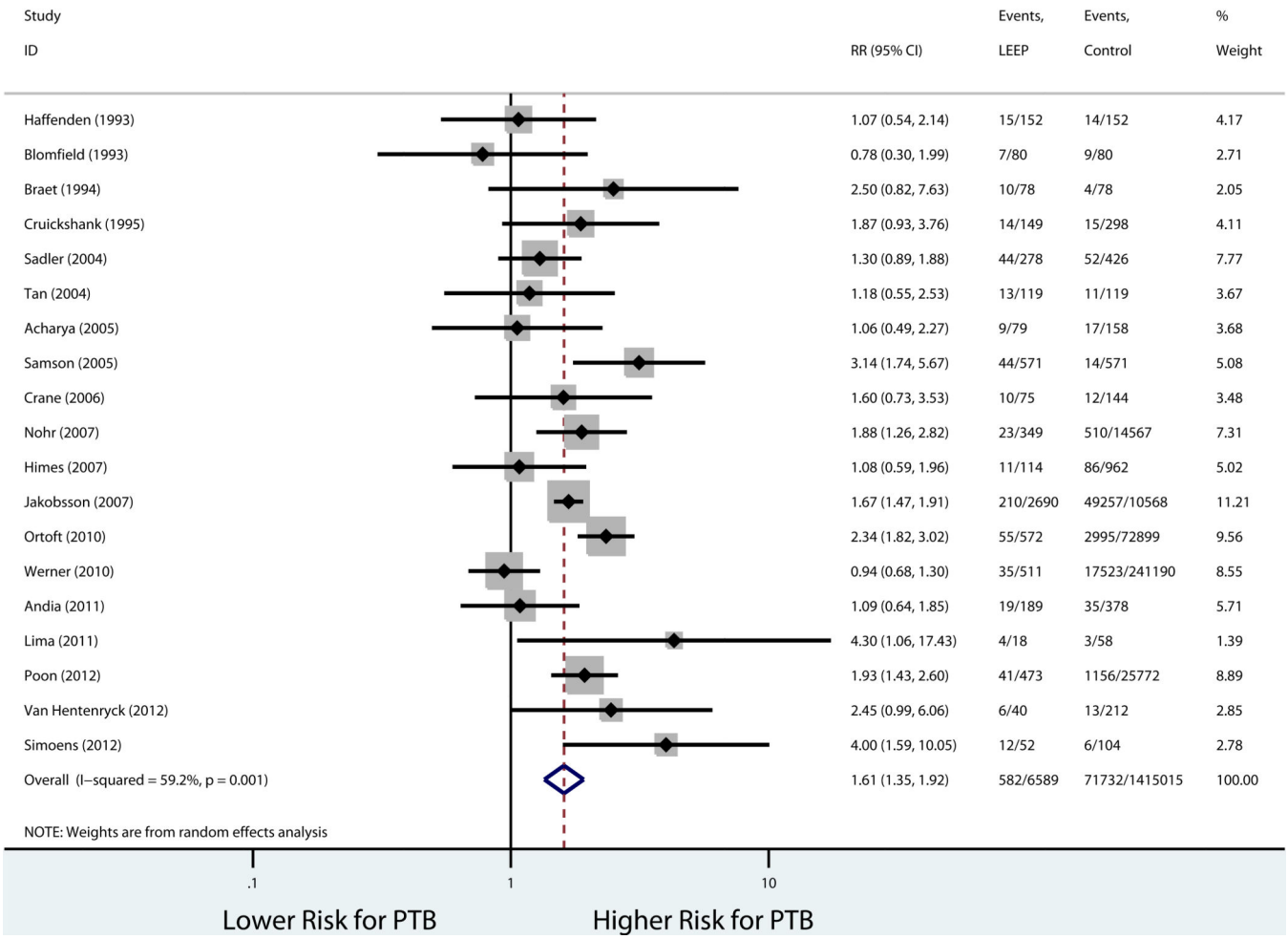

Figure 2.
Forest Plot LEEP and PTB <37 weeks

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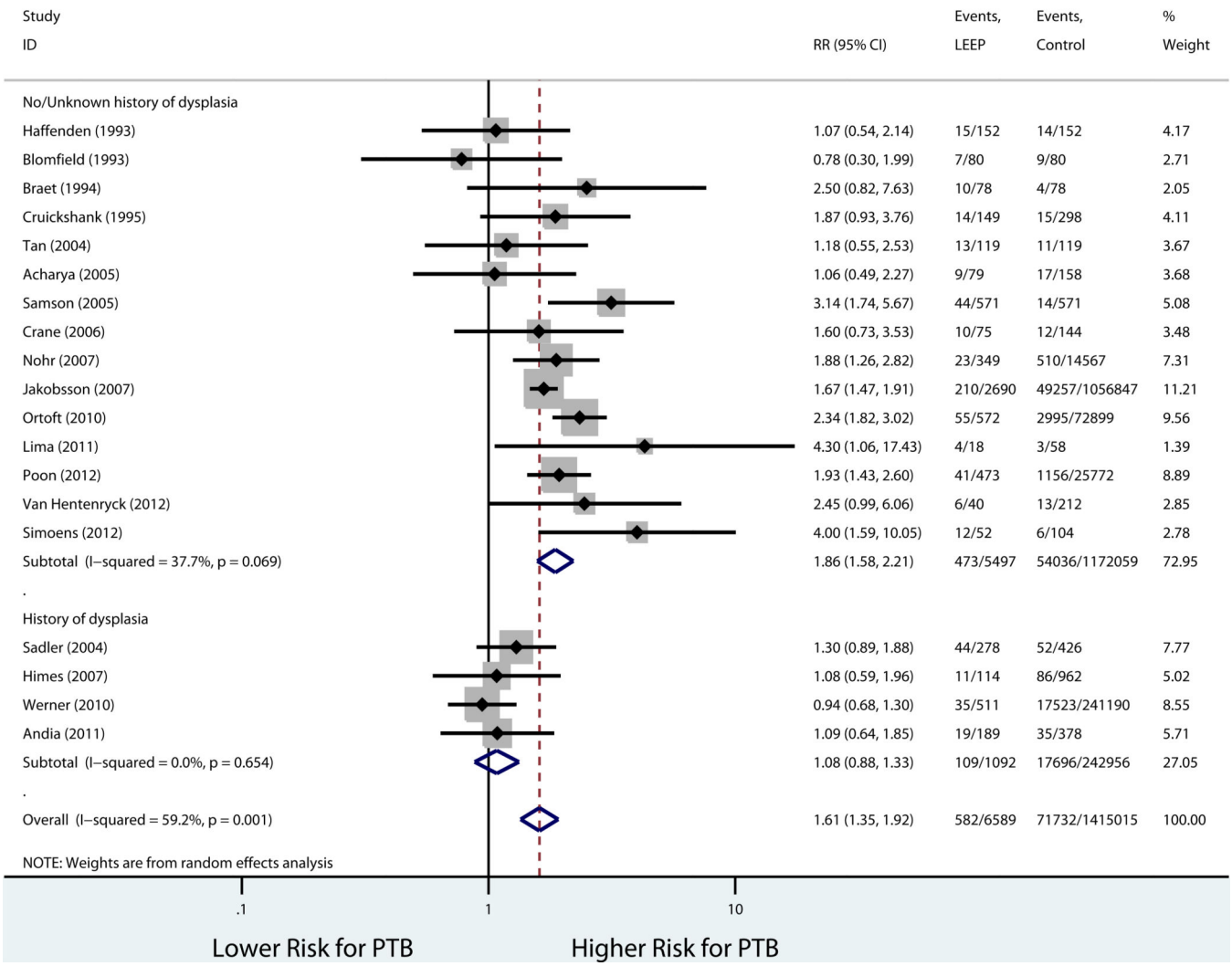

Figure 3.
Forest Plot LEEP and PTB stratified by unexposed group

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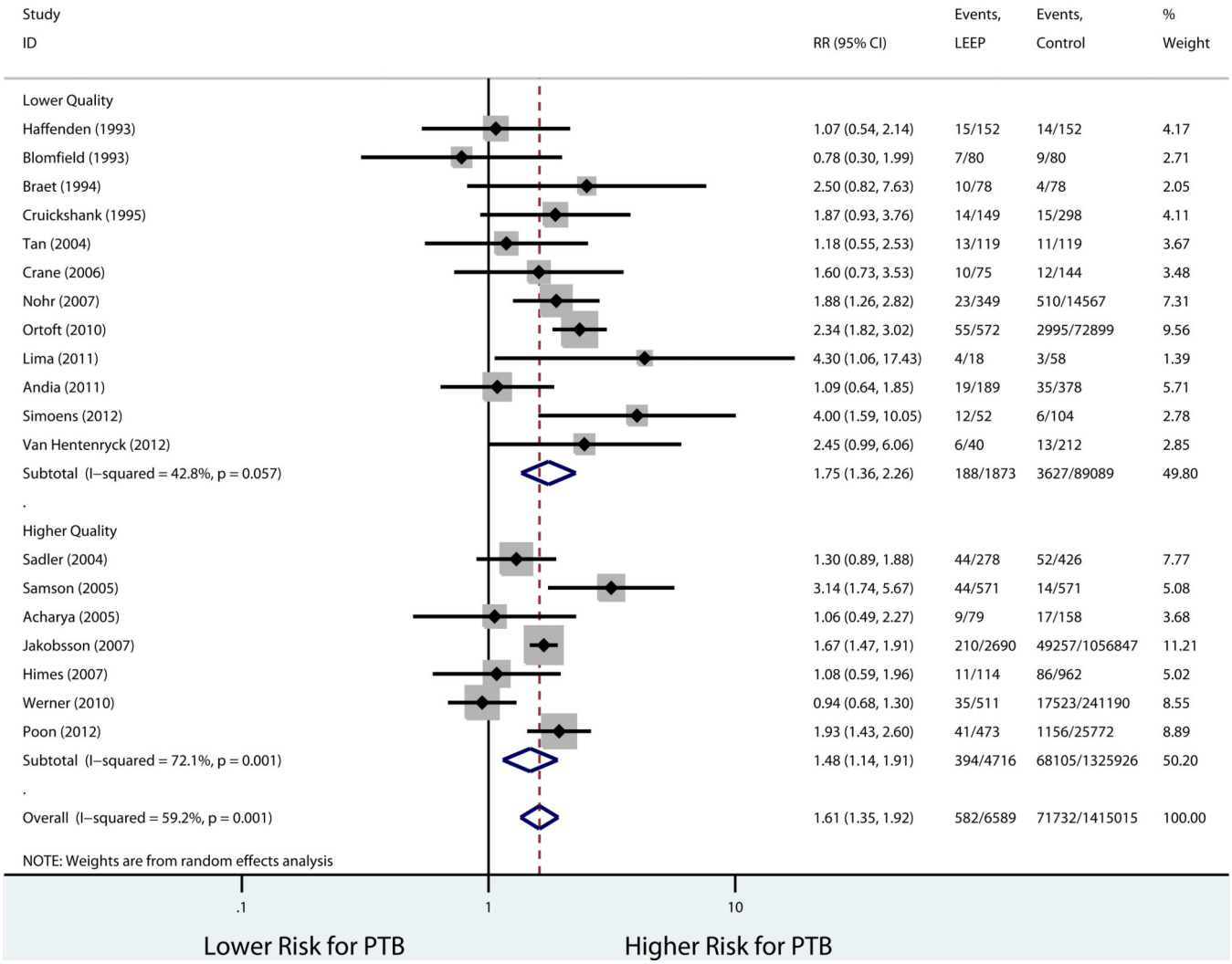

Figure 4.
Forest plot LEEP and PTB stratified by study quality

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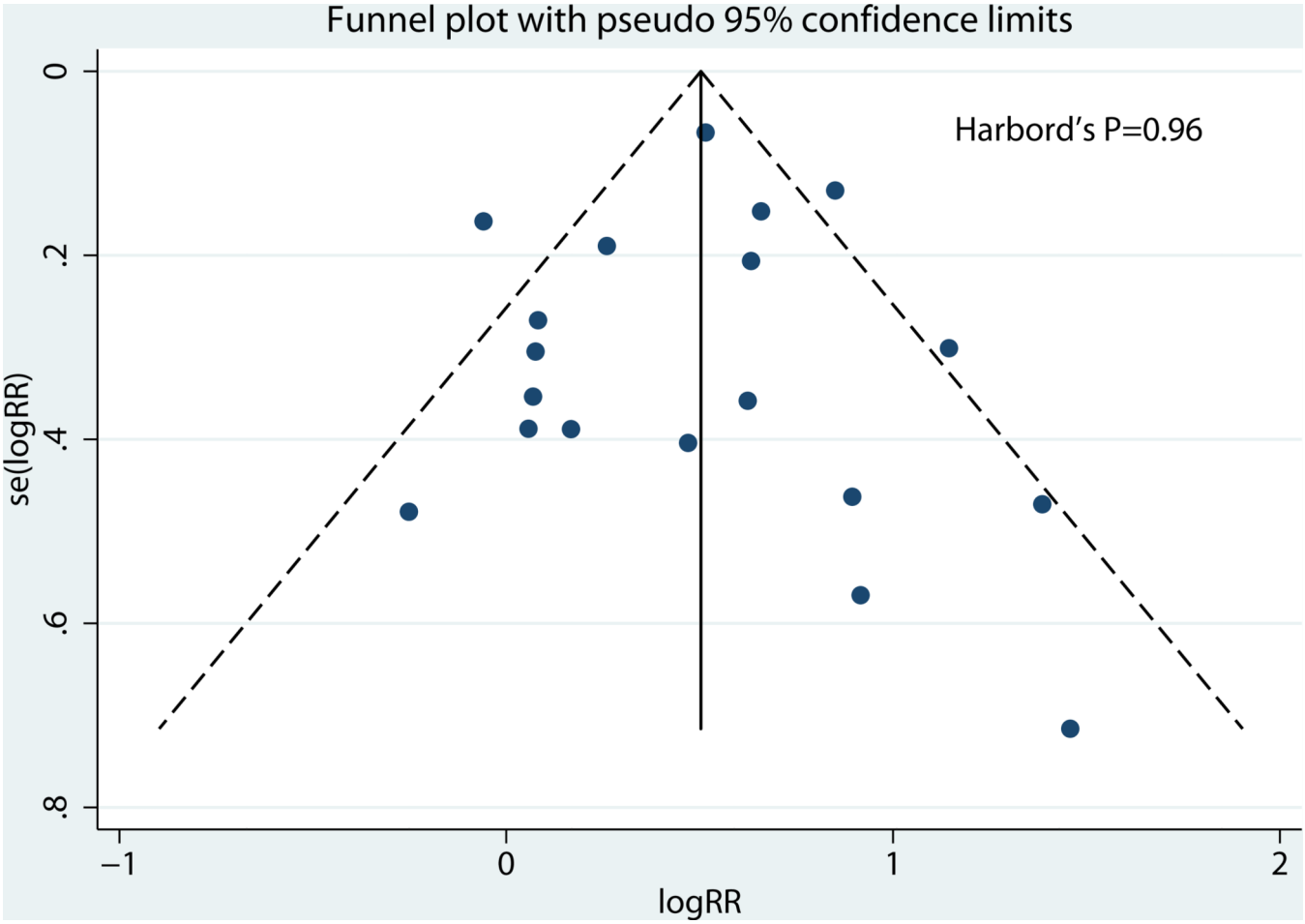

Figure 5.
Funnel plot, Publication Bias

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Table 1

Characteristics of Included Studies

Study	Year	Country	Study Design	Inclusion Criteria	Exclusion Criteria	LEEP (n)	Unexposed
Haffenden	1993	UK	Retrospective cohort	Pregnancy post-LEEP	Birth < 24 weeks	*152*	Unknown dysplasia hx, no prior tx *N= 152*
Blomfield	1993	UK	Retrospective cohort	Pregnancy post-LEEP	Birth < 20 weeks	*40*	Unknown dysplasia hx, no prior tx *N= 80*
Braet	1994	UK	Retrospective cohort	*1st* pregnancy post-LEEP	Multiple gestation	*78*	Unknown dysplasia hx, no prior tx *N= 78*
Cruickshank	1995	UK	Retrospective cohort	*1st* pregnancy post-LEEP	Birth < 20 weeks, multiple gestation	*149*	Unknown dysplasia hx, no prior tx *N= 298*
Sadler	2004	New Zealand	Retrospective cohort	*1st* pregnancy post-LEEP	Birth < 20 weeks, multiple gestation, LEEP during pregnancy	*278*	Prior dysplasia, no prior tx *N=426*
Tan	2004	UK	Retrospective cohort	*1st* pregnancy post-LEEP	Age > 35 years	*119*	Unknown dysplasia hx, no prior tx *N= 119*
Acharya	2005	Norway	Retrospective cohort	*1st* pregnancy post-LEEP	Age >45 years, birth <20 weeks	*79*	Unknown dysplasia hx, no prior tx *N= 158*
Samson	2005	Canada	Retrospective cohort	*1st* pregnancy post-LEEP	Birth < 20 weeks, multiple gestation, prior PTB, indicated deliveries	*571*	Unknown dysplasia hx, no prior tx *N=571*
Crane	2006	Canada	Prospective cohort	Pregnancy post-LEEP	Multiple gestation	*75*	Unknown dysplasia hx, no prior tx *N= 144*
Nohr	2007	Denmark	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation, indicated deliveries, stillbirth	*349*	Unknown dysplasia hx, no prior tx *N= 14,567*
Himes	2007	USA	Retrospective cohort	*1st* pregnancy post-LEEP	Birth < 20 weeks, multiple gestation, anomalies, LEEP during pregnancy	*114*	Prior dysplasia, no prior tx *N= 962*
Jakobsson	2007	Finland	Retrospective cohort	Pregnancy post-LEEP	Age > 49 years, age < 15 years, multiple gestation	*2690*	Unknown dysplasia hx, no prior tx *N= 1,056,855*
Ortoft	2010	Denmark	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation, indicated deliveries	*572*	No hx of dysplasia or prior tx *N=72,899*
Werner	2010	USA	Retrospective cohort	*1st* pregnancy post-LEEP	Multiple gestation, LEEP during pregnancy	*511*	Unknown dysplasia hx, no prior tx *N= 240,348* Prior dysplasia, no prior tx *N= 842*
Andia	2011	Spain	Retrospective cohort	Pregnancy post-LEEP	Multiple gestation	*189*	Unknown dysplasia hx, no prior tx *N= 189* Prior dysplasia, no prior tx *N= 189*

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Study	Year	Country	Study Design	Inclusion Criteria	Exclusion Criteria	LEEP (n)	Unexposed
Lima	2011	Portugal	Retrospective cohort	Pregnancy post-LEEP	None	*18*	Unknown dysplasia hx, no prior tx *N= 58*
Poon	2012	UK	Case control	Pregnancy post-LEEP	Multiple gestation, cerclage, anomalies, preterm PROM, contractions, progesterone, indicated deliveries	*473*	Unknown dysplasia hx, no prior tx *N= 25,772*
Van Hentenryck	2012	Belgium	Retrospective cohort	Pregnancy post-LEEP	None	*40*	Unk dysplasia hx, no prior tx *N= 212*
Simoens	2012	Belgium	Prospective cohort	Pregnancy post – EEP	Birth < 20 weeks, multiple gestation	*52*	No hx of dysplasia or prior tx *N= 104*

LEEP, loop electrosurgical excision procedure; hx, history; tx, treatment; PROM, premature rupture of membranes.

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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

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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 Relative Risk	95% CI	Heterogeneity	
						Cochran's *P* value	I^2
PTB <37 wks	19	8.8% (582/6549)	5.1% (71732/1415023)	1.61	1.35–1.92	0.001	59.2%
Stratified by study unexposed group							
No/unknown hx of dysplasia	15	8.6% (473/5457)	4.6% (54036/1172059)	1.86	1.58–2.21	0.069	37.7%
Hx of dysplasia	4	10.0% (109/1092)	7.2% (17696/242946)	1.08	0.88–1.33	0.654	0.00%
Stratified by Study Quality							
Lower	12	10.3% (188/1833)	4.1% (3627/89089)	1.75	1.36–2.26	0.057	42.8%
Higher	7	8.4% (394/4716)	5.1% (68105/1325926)	1.48	1.14–1.91	0.001	72.1%
Spontaneous PTB<37 wks	8	6.8% (147/2175)	3.4% (11684/342097)	1.60	0.99–2.55	<0.001	73.6%
Preterm PROM	6	5.1% (108/2102)	2.5% (7940/314891)	2.37	1.64–3.44	0.094	46.9%
PTB<34 wks	5	2.9% (48/1670)	2.3% (6053/267889)	2.21	1.33–3.67	0.157	39.6%
Perinatal mortality	7	1.0% (19/1925)	0.8% (2496/315118)	1.63	0.95–2.80	0.911	0.00%

CI, confidence interval; PTB, preterm birth; hx, history; PROM, premature rupture of membranes.

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