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The risk of preterm birth of treated versus untreated cervical intraepithelial neoplasia (CIN): a systematic review and meta-analysis

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ABSTRACT

Background: Cervical surgery is associated with preterm birth (PTB) and neonatal morbidity. However, it is unknown whether this increased risk is due to the surgery itself or to the cervical intraepithelial neoplasia (CIN) or underlying the surgery. Our objective was to asses the risk for PTB in women with treated and untreated CIN.

Methods: We performed an electronic literature search in MEDLINE, Embase and CENTRAL for studies that reported on pregnancy outcome after treated and untreated CIN. The methodological quality was scored using the STROBE combined checklist for observational studies. We extracted data on PTB<37 weeks, very PTB<32 weeks, spontaneous PTB<37 weeks, (preterm) premature rupture of membranes ((P)PROM), perinatal mortality and section caesarean each before and after treatment for CIN. We used the Mantel-Haenszel method to estimate summarizing odds ratios.

Results: Our search identified 620 studies, of which 20 were reporting on pregnancy outcome for a total of 12,159,293 women. There were 20,832 women who gave birth after treatment for CIN before pregnancy, 52 women who gave birth after treatment for CIN during pregnancy, 64,237 women with CIN who gave birth before treatment, and 8,902,865 women who gave birth without CIN. Compared to women with untreated CIN, women treated for CIN before or during pregnancy, had a significantly higher risk of PTB<37 weeks (OR 1.7, 95% CI 1.0-2.7). When comparing women treated for CIN *before* pregnancy (*n*=20,832) to women with untreated CIN (*n*=64,162), we found an OR of 1.4 with a 95% confidence interval of 0.85 to 2.3. Women treated during pregnancy had a clearly increased risk for PTB (OR 6.5, 95% CI 1.1 to 37), and (P)PROM (OR 1.8, 95% CI 1.4 to 2.2). In women with cervical surgery. the risks for *spontaneous* PTB<37 weeks (OR0.87, 95% CI 0.54-1.4), Caesarean Section (OR1.0, 95% CI 0.71-1.5) and perinatal mortality (OR 1.0, 95% CI0.38-2.8) were not increased.

Conclusion: The increased risk of PTB in women who underwent cervical surgery for CIN is especially increased when performed *during p*regnancy. When performed before pregnancy the risk of PTB is increased, although insignificant.

INTRODUCTION

Preterm birth (PTB) is the leading cause of neonatal morbidity and mortality in the Western world, accounting for approximately 75% of all neonatal deaths.[1] The incidence of PTB varies between countries, the USA having a relatively high rate (12-13%), while countries such as the Netherlands (7.1%) and Scandinavia (6.1%) have lower rates.[1-3] Recent studies have shown that treatment for cervical intraepithelial neoplasia (CIN) is associated with an increased risk of PTB and subsequent poor pregnancy outcome.[4,5] This is of importance, as worldwide screening programs have been introduced that aim at early detection of cervical cancer and a reduction of cervical cancer related mortality, thus affecting women during their reproductive age.

The age at which screening starts varies between countries: In the Netherlands, for example, women are invited for screening from the age of 30 with a 5-year interval. In The United States screening starts much earlier: the American College of Obstetricians and Gynaecologists (ACOG) recommends to start screening at age 21 years with a 3-year interval.[6] In the United Kingdom screening starts at age 20 to 25 with a 3 to 5 year interval.[7] When screening leads to detection of a CIN II or CIN III lesion most women will be treated with a large loop excision of the transformation zone (LLETZ).[8] As a consequence, screening for cervical cancer in younger women might not only reduce cervical cancer, but also increase the risk of PTB. However, instead of being related to cervical surgery PTB might also be related to CIN itself or maybe even to an underlying communal disorder resulting both in CIN and PTB, thus potentially confounding the association between cervical surgery and PTB. To address this issue, we conducted a systematic review and meta-analysis, in which we compared pregnancy outcomes between women with CIN who have been treated before pregnancy, treated during pregnancy, or not treated as well as women without CIN.

METHODS

Search and selection

This systematic review was conducted according to PRISMA guidelines. A medical librarian (J.L.) searched the following databases from inception to January 07, 2014: OVID MEDLINE, OVID Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), complemented with a search of PubMed to find recent studies not in MEDLINE. The search strategy consisted of Subject Headings (MeSH in MEDLINE)

and words in title and abstract for CIN and pregnancy outcome (including PTB, premature rupture of membranes (PROM), birth weight and secondary outcomes). We combined a search for CIN with a broad search for PTB including PROM and birth weight and secondary outcomes, such as perinatal mortality, Apgar score and mode of delivery. In MEDLINE we also searched for cervical surgery and PTB only, aiming to find papers about CIN treatment not mentioning CIN in the abstract (see Appendix SI for the complete MEDLINE search strategy).
The search included an iterative process to refine the search strategy through adding search terms as new relevant citations were identified, i.e. by checking reference lists and citing articles using ISI Web of Science. Reference Manager® software (version 12.0) was used to manage and de-duplicate all identified references.
No language restrictions were applied. We used native speakers to extract data from papers in German or other languages we could not assess ourselves.

All studies that examined PTB or adverse neonatal outcome in women with known CIN were eligible. We excluded conference abstracts and editorials. We included studies using study and control groups defined as treated and untreated CIN, as well as post- and preconisation delivery and women with and without CIN. PTB was stratified as birth before 32 and 37 weeks gestation, respectively. Spontaneous PTB was defined as PTB not due to induction of labour.[9] The cases in which PTB is due to induction of labour, we defined as "iatrogenic PTB". When severity of dysplasia was not reported, we assumed that women undergoing cervical excision after a delivery already had CIN at time of delivery.
Two investigators (ND, EK) independently reviewed titles, abstracts and full text articles and selected the studies. Any disagreements were resolved by discussion until consensus was reached.

Quality assessment

The methodological quality of the included studies was evaluated independently by two researchers (ND, EK) using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) combined checklist for observational studies (2007, version 4).[10] This checklist consists of 22 items that relate to the article's title and abstract, the introduction, methods, results, discussion and other information on conflicts of interest and funding. The checklist has been developed to provide guidance on how to report observational research well, but is being used as a rating scale for the evaluation of quality as well.[11,12] Of the 22 items we did not use the one on sample size as we expected to include only observational studies which do usually not include sample size calculations. The item on adjustment for

confounders was scored as present if one of the following items was controlled for: age, smoking status or prior PTB.
Studies were considered as 'high quality', 'moderate quality' or 'low quality', when they met 100% to 80%, 79% to 50% or less than 50% of the items, respectively. Data on pregnancy outcomes, i.e. gestational age at time of delivery, (preterm) premature rupture of membranes ((P)PROM), section caesarean rate, perinatal mortality were recorded using a specially designed template.

Statistical analysis

RevMan software from the Cochrane Collaboration version 5.2 was used for meta-analysis. We calculated odds ratios (ORs) and 95% confidence intervals (CI) on the risk of PTB in women with untreated CIN compared to women treated for CIN or in women without CIN. In the analysis we assessed the following endpoints: PTB before 37 weeks gestational age, very PTB before 32 weeks gestational age, spontaneous PTB before 37 weeks, (P)PROM, perinatal mortality and section caesarean. We compared women who were treated for CIN before or during pregnancy to women with untreated CIN. If data were available, we also compared women diagnosed with CIN to healthy women.
We constructed forest plots, and assessed heterogeneity using both the Higgens I^2 test as well as eye ball assessment.[13] With the eyeball test we looked for overlap of the confidence intervals of the included studies in the meta-analysis. If the I^2test indicated heterogeneity ($P<0.1$ and $I^2>50\%$), a random effects model was used, while if homogeneity could not be rejected ($P>0.1$ and $I^2<50\%$), pooling was done with a fixed effects model.

RESULTS

Selection of studies

The systematic search yielded 620 articles, of which 587 were excluded after screening title and abstract. We screened the full text of 33 records, of which 13 articles were excluded due to the following reasons: editorial letter (*n*=2), study population does not contain women with CIN (*n*=6), pregnancy outcomes not described (*n*=4), no comparison between women with CIN, women treated for CIN or healthy women (*n*=1). The remaining 20 studies were considered eligible (figure 1). Of these 20 remaining studies, 19 were cohort studies and 1 was a case-control study.

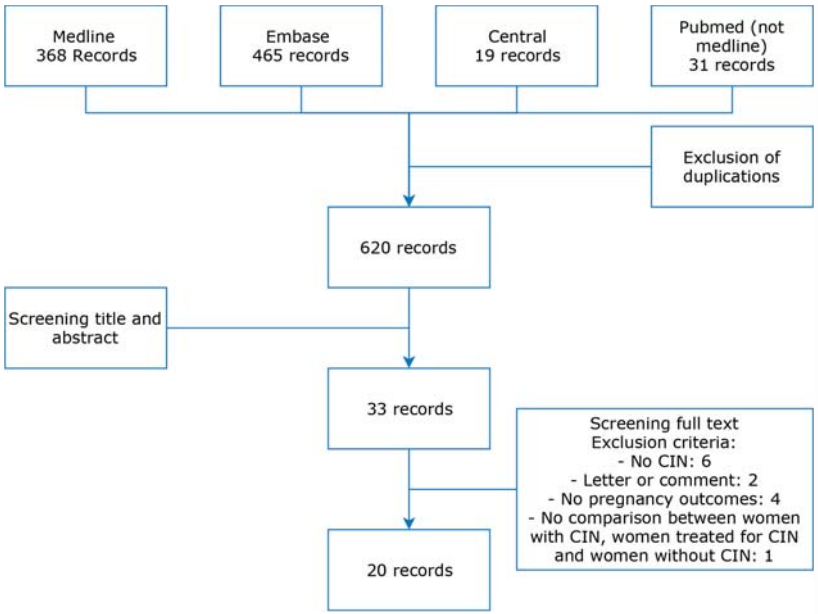


Figure 1: Flowchart of search strategy.
CIN, cervical intraepithelial neoplasia.

Methodological quality

Table 1 provides an overview of the methodological quality and the extracted data. The included studies were published between 1993 and 2013. A total of 15 studies compared women with treatment for CIN to women with untreated CIN. Three of these studies reported on women treated for CIN *during* pregnancy, while the other 12 studies report on treatment before pregnancy. Four studies compared women with untreated CIN to women without CIN. After quality assessment 9 studies (45%) scored high quality, 10 (50%) scored moderate quality and 1 (5%) scored low quality.

Table 1: Key characteristics and quality assessment of the included studies

Study	Study/controle groups	No. of patients in groups	Outcome measures				Factors maximally adjusted for	Quality assesment
			Preterm birth	PPROM	SC	Perinatal mortality		
Albrechtsen 2008	Post-conisation delivery	15,108	24-27 weeks	No	No	No	Age Birth order 1 vs > 1	**High**
	Pre-conisation delivery	57,136	28-32 weeks					
	No conisation	2,164,006	33-36 weeks					
			< 37 weeks					
Andia 2011	Post-conisation delivery	189	< 32 weeks	No	Yes	No	No adjustments	**Moderate**
	Pre-conisation delivery	189	< 35 weeks					
	No conisation	189	< 37 weeks					
Al-Halal 2013	Women without CIN	8,814,088	< 37 weeks	Yes	Yes	No	Age Hospital type Race Reported income Type of insurance	**High**
	Women with CIN	11,755						
	Cervical cancer	294						
Bruinsma 2007	Treated CIN	1,951	< 37 weeks	Yes	Yes	Yes	Age Drug use during pregnancy Hospital birth Induced abortion Marital status Maternal medical condition Miscarriage Prior PTB Treatment for CIN	**High**
	Untreated CIN	3,597	Spontaneous PTB					
El –Bastawissi 1999	Untreated CIN	1,834	<37 weeks	No	Yes	No	Smoking Race Parity Martial status History of induction	**High**
	Treated CIN	9,201	<34 weeks					

Table 1: Continued

Study	Study/controle groups	No. of patients in groups	Outcome measures				Factors maximally adjusted for	Quality assesment
			Preterm birth	PPROM	SC	Perinatal mortality		
Himes 2007	Treated CIN Untreated CIN	114 962	< 37 weeks Spontaneous PTB	Yes	No	No	Age Height of the cone specimen Marital status Payor status Prior PTB Race Tobacco use Years of education	**High**
Jakobsson 2009	Post-conisation delivery Pre-conisation delivery Women in the Medical Birth register	258 258 544,507	< 37 weeks	No	No	No	Age Parity	**High**
Kalitsaris 1991	Post-conisation delivery Pre-conisation delivery	42 59	< 37 weeks	No	No	No	No adjustments	**Moderate**
Kristensen 1993	Post-conisation delivery Pre-conisation delivery No conisation Conisation between deliveries	34 74 14,062 62	< 37 weeks	No	No	No	No adjustments	**Moderate**
Larsson 1982	Post-conisation delivery Pre-conisation delivery	294 341	< 36 weeks	No	Yes	Yes	No adjustments	**Moderate**
Ortoft 2010	Post-conisation delivery Pre-conisation delivery No conisation	383 746 72,899	< 28 weeks < 32 weeks < 37 weeks	Yes	No	Yes	Age Educational level Marital status Parity Smoking status	**High**

Table 1: Continued

Study	Study/controle groups	No. of patients in groups	Outcome measures				Factors maximally adjusted for	Quality assesment
			Preterm birth	PPROM	SC	Perinatal mortality		
Rosen 1991	Treated CIN Untreated CIN	30 33	< 35 weeks	No	No	No	No adjustments	**Moderate**
Sadler 2004	Treated CIN Untreated CIN	652 426	< 32 weeks < 37 weeks Spontaneous PTB	Yes	No	No	Age Ethnicity Prior PTB Smoking during pregnancy Transfer to National Women's Hospital	**High**
Sagot 1995	Post-coniston delivery Pre-conisaton delivery	53 59	< 37 weeks	Yes	No	No	No adjustments	**Low**
Shanbhag 2009	Treated CIN Untreated CIN General population	1,103 87 119,216	< 37 weeks Spontaneous PTB	Yes	Yes	Yes	Age Birth weight Year of delivery Deprivation level Smoking before pregnancy Malpresentation Preterm labor PROM Sectio Secarean	**High**
Smaldone 2010	Women without CIN Women with CIN 3 and cervical cancer	78,087 135	< 37 weeks	Yes	Yes	Yes	Age Gestational hypertension Medicaid insurance Race	**Moderate**
Sljivancanin 2013	Treated CIN Untreated CIN	10 48	< 37 weeks	No	No	No	No adjustments	**Moderate**
Torres 2013	Women without CIN Women with CIN	2,000 42	< 34 weeks < 37 weeks	No	No	No	No adjustments	**Moderate**

Table 1: Continued

Study	Study/controle groups	No. of patients in groups	Outcome measures				Factors maximally adjusted for	Quality assesment
			Preterm birth	PPROM	SC	Perinatal mortality		
Werner 2010	Post-conisation delivery	511	< 33 weeks	Yes	No	Yes	Age	**Moderate**
	Pre conisation delivery	842	34-36 weeks				Nulliparity	
	General population	240,348	< 37 weeks				Race	
			Spontaneous PTB					
Zuo 2011	Women without CIN	715	< 37 weeks	No	No	No	No adjustments	**Moderate**
	Women with CIN	264						

(P)PROM = (preterm) premature rupture of membranes; PTB = preterm birth; IUGR = intrauterine growth restriction; SGA = small for gestational age; SC = section cesarean

Synthesis of results and meta-analysis

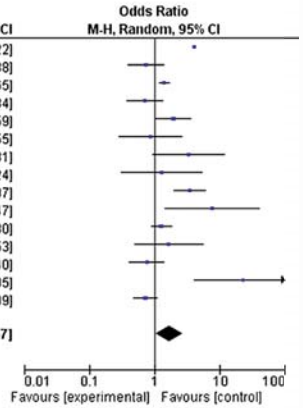
As shown in table 1, the included studies used different selection criteria for the study and control groups. We grouped "post-conisation delivery" and "treated CIN" together, as well as "pre-conisation delivery" and "untreated CIN." We also clustered "healthy women," "women without CIN" and the "general population" into one control group.

To estimate the association between treatment of CIN and the risk of PTB before 37 weeks, we compared women treated for CIN to women with untreated CIN. Fifteen studies reported on PTB 14 of these defined PTB as birth before 37 weeks gestational age [14-16, 18-28] but we also included one study, [29] which defined PTB as birth before 36 weeks of gestational age. These 15 studies described the pregnancy outcome for 20,884 women treated for CIN and 64,237 women with untreated CIN (figure 2A). With the random effects model we calculated the risk of PTB before 37 weeks, which was significant higher in women treated for CIN (OR 1.7, 95% CI 1.0-2.7). Women treated for CIN *during* pregnancy (*n*=52) had an increased risk as compared to women with untreated CIN (*n*=458) OR of 6.5 (95% CI of 1.1-37) (figure 2B). When comparing women treated for CIN *before* pregnancy (*n*=20,832) to women with untreated CIN (*n*=64,162), we found an OR of 1.4 with a 95% confidence interval of 0.85 to 2.3 (figure 2C).

A. Comparing women treated for CIN to women with untreated CIN

Study or Subgroup	Treated CIN Events	Total	Untreated CIN Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albrechtsen 2008	2599	15108	2828	57136	8.5%	3.99 [3.77, 4.22]
Andia 2011	19	189	25	189	7.4%	0.73 [0.39, 1.38]
Bruinsma 2007	224	1951	309	3597	8.4%	1.38 [1.15, 1.65]
Himes 2007	11	114	127	962	7.4%	0.70 [0.37, 1.34]
Jakobsson 2009	31	258	17	258	7.5%	1.94 [1.04, 3.59]
Kalitsaris 1991	7	55	8	55	5.9%	0.86 [0.29, 2.55]
Kristensen 1993	6	28	5	65	5.2%	3.27 [0.91, 11.81]
Larsson 1982	4	82	4	103	4.8%	1.27 [0.31, 5.24]
Ortoft 2010	91	746	15	383	7.6%	3.41 [1.95, 5.97]
Rosen 1991	9	24	2	27	4.2%	7.50 [1.43, 39.47]
Sadler 2004	97	652	52	426	8.1%	1.26 [0.88, 1.80]
Sagot 1995	7	53	5	59	5.5%	1.64 [0.49, 5.53]
Shanbhag 2009	129	1103	13	87	7.5%	0.75 [0.41, 1.40]
Sljivancanin 2013	6	10	3	48	4.0%	22.50 [4.02, 125.95]
Werner 2010	35	511	78	842	8.0%	0.72 [0.48, 1.09]
Total (95% CI)		**20884**		**64237**	**100.0%**	**1.67 [1.04, 2.67]**
Total events	3275		3491			

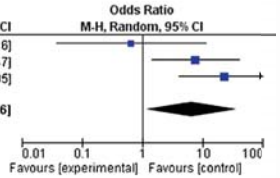
Heterogeneity: Tau² = 0.68; Chi² = 296.00, df = 14 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.12 (P = 0.03)



B. Comparing women treated for CIN *during* pregnancy to women with untreated CIN

Study or Subgroup	Treated during pregnancy Events	Total	Untreated Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ortoft 2010	0	18	15	383	23.1%	0.64 [0.04, 11.16]
Rosen 1991	9	24	2	27	38.9%	7.50 [1.43, 39.47]
Sljivancanin 2013	6	10	3	48	37.9%	22.50 [4.02, 125.95]
Total (95% CI)		**52**		**458**	**100.0%**	**6.45 [1.12, 37.16]**
Total events	15		20			

Heterogeneity: Tau² = 1.33; Chi² = 4.59, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 2.09 (P = 0.04)



C. Comparing women treated for CIN *before* pregnancy to women with untreated CIN

Study or Subgroup	Treated CIN Events	Total	Untreated CIN Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albrechtsen 2008	2599	15108	2828	57136	9.3%	3.99 [3.77, 4.22]
Andia 2011	19	189	25	189	8.1%	0.73 [0.39, 1.38]
Bruinsma 2007	224	1951	309	3597	9.2%	1.38 [1.15, 1.65]
Himes 2007	11	114	127	962	8.0%	0.70 [0.37, 1.34]
Jakobsson 2009	31	258	17	258	8.1%	1.94 [1.04, 3.59]
Kalitsaris 1991	7	55	8	55	6.4%	0.86 [0.29, 2.55]
Kristensen 1993	6	28	5	65	5.7%	3.27 [0.91, 11.81]
Larsson 1982	4	82	4	103	5.3%	1.27 [0.31, 5.24]
Ortoft 2010	91	728	15	383	8.3%	3.50 [2.00, 6.14]
Sadler 2004	97	652	52	426	8.9%	1.26 [0.88, 1.80]
Sagot 1995	7	53	5	59	5.9%	1.64 [0.49, 5.53]
Shanbhag 2009	129	1103	13	87	8.1%	0.75 [0.41, 1.40]
Werner 2010	35	511	78	842	8.7%	0.72 [0.48, 1.09]
Total (95% CI)		**20832**		**64162**	**100.0%**	**1.39 [0.85, 2.28]**
Total events	3260		3486			

Heterogeneity: Tau² = 0.68; Chi² = 290.39, df = 12 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.32 (P = 0.19)

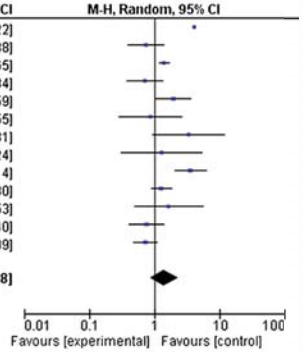
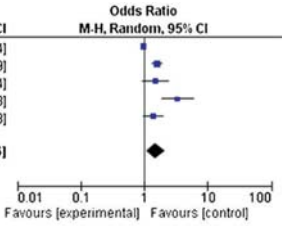


Figure 2: Forest plot of preterm birth < 37 weeks (iatrogenic PTB and spontaneous PTB).

Five studies compared the risk of PTB before 37 weeks for women diagnosed with CIN without treatment (13,754 women) with healthy women (8,902,865 women) (figure 3).[17,30-33] Women with untreated CIN had a higher risk of PTB (OR 1.5, 95%CI 1.1-2.2).

Study or Subgroup	CIN Events	Total	no CIN Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Halal 2012	817	11755	630207	8814088	24.4%	0.97 [0.90, 1.04]
El Bastawissi 1999	187	1541	637	7975	23.3%	1.59 [1.34, 1.89]
Smaldone 2010	22	135	9058	78087	17.5%	1.48 [0.94, 2.34]
Torres 2013	18	59	235	2000	15.0%	3.30 [1.86, 5.83]
Zuo 2011	56	264	116	715	19.8%	1.39 [0.97, 1.98]
Total (95% CI)		**13754**		**8902865**	**100.0%**	**1.51 [1.06, 2.16]**
Total events	1100		640253			

Heterogeneity: Tau² = 0.13; Chi² = 46.60, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.29 (P = 0.02)



CIN = cervical intraepithelial neoplasia; PTB = preterm birth; CI = confidence interval, M-H = Mantel-Haenszel

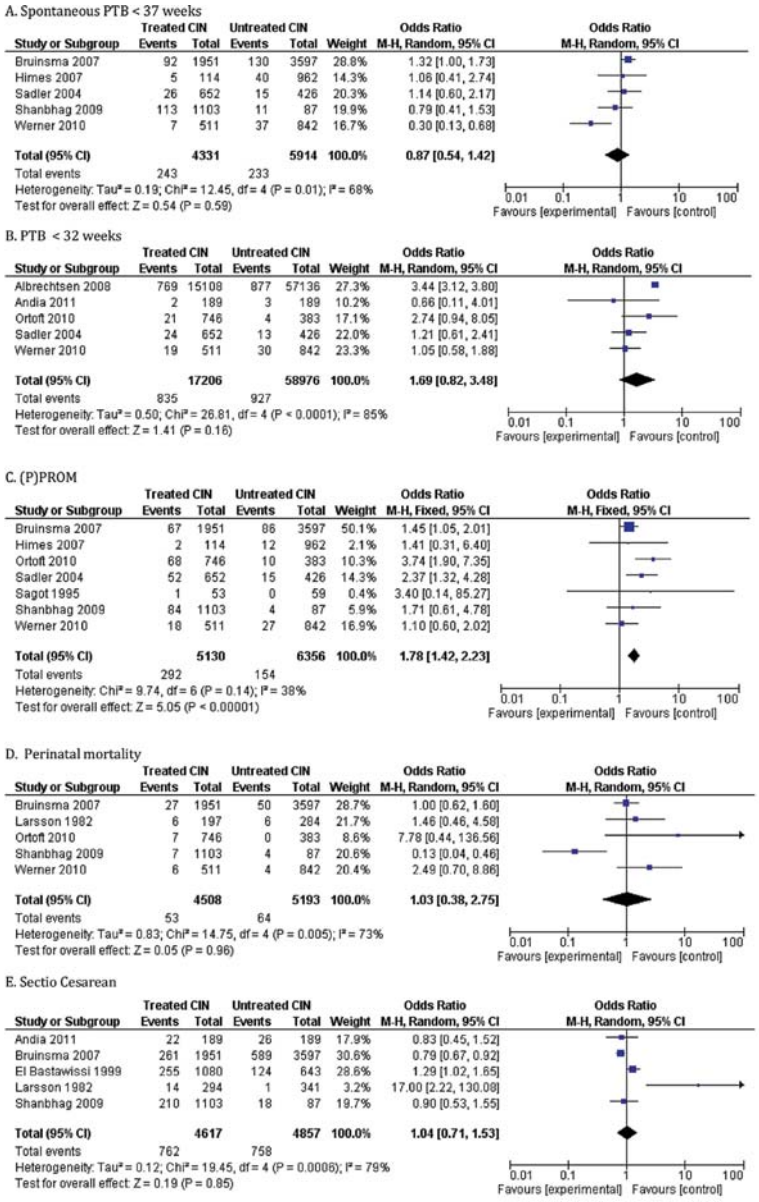
Figure 3: Forest plot of preterm birth < 37 weeks.
Comparing women with untreated CIN to women being without a CIN diagnosis.

Five studies compared women treated for CIN (*n*=4,331) to women with untreated CIN (*n*=5,914) for *spontaneous* PTB before 37 weeks (figure 4A).[16,18,24,26,28] A random effects model showed no increase in *spontaneous* PTB before 37 weeks (OR0.87, 95 %CI 0.54-1.4).

Five studies estimated the risk of very PTB in 17,206 women treated for CIN versus 58,976 women with untreated CIN. Four studies[14,15,22,24] defined very preterm birth as PTB before 32 weeks and one study as PTB before 33 weeks.[28] All five were for this analysis (OR1.7, 95%CI 0.82-3.5, random effects model) (figure 4B).

Seven studies reported on (P)PROM.[16,17,22,24-26,28] A total of 5,130 women treated for CIN were included and 6,356 women with untreated CIN and showed a significant increased risk of PPROM after treatment (OR1.8, 95%CI 1.4 to 2.2) (figure 4C).

Perinatal mortality did not differ in 4,508 women treated for CIN and 5,193 women with untreated CIN included in 5 studies (figure 4D) [16,22,26,28,29] The caesarean section rate was reported in five studies.[15-17,26,29] We found no difference between women treated for CIN (*n*=4,617) and women with untreated CIN (*n*=4,857) (OR1.0, 95%CI 0.71-1.5).



CIN = cervical intraepithelial neoplasia; PTB = preterm birth; CI = confidence interval, M-H = Mantel-Haenszel

Figure 4: Forest plot of A. spontaneous preterm birth < 37 weeks, B. preterm birth < 32 weeks, C. (P)PROM and D.perinatal mortality, E Sectio Cesarean

The Higgens I^2 test showed statistical heterogeneity among the studies included in the following analyses, while by eyeballing the confidence intervals of the majority of the studies overlapped: PTB before 37 weeks comparing women treated for CIN to women with untreated CIN (P<0.1, I^2=95%, CI overlapped in 73% of the studies), PTB before 37 weeks comparing women with CIN to women without CIN (P<0.1, I^2=91%, CI overlapped in 80% of the studies), *spontaneous* PTB before 37 weeks (P=0.01, I^2=68%, CI overlapped in 80% of the studies), very PTB (P<0.1, I^2=85%, CI overlapped in 80% of the studies), perinatal mortality (P<0.1, I^2=73%, CI overlapped in 80% of the studies) and the section caesarean rate (P<0.1, I^2=79%, CI overlapped in 80% of the studies). There was no heterogeneity among the studies included in the analysis on the risk of (P)PROM (P=0.14, I^2=38%, CI overlapped in 100% of the studies).

DISCUSSION

Main findings

In this meta-analysis, we identified 20 studies examining pregnancy outcomes in 20,884 women delivering after treatment for CIN, 64,237 women delivering with untreated CIN and 8,902,865,women giving birth without CIN.

We found that women treated for CIN compared to women with untreated CIN have a significant higher risk of PTB before 37 weeks. This was mainly attributed to treatment performed *during* pregnancy. However, women treated for CIN before pregnancy also had an increased risk, albeit it not statistically significant. Moreover, women treated for CIN are at significantly increased risk of (P)PROM. The risk of very PTB before 32 weeks also seemed to be increased in women treated for CIN outside of pregnancy compared to women with untreated CIN, although the difference did not reach statistical significance. Studies did neither report an increased risk of *spontaneous* PTB, section caesarean nor on perinatal mortality.

Strengths and limitations

Recent studies have shown that treatment for CIN is associated with an increased risk of PTB and subsequent poor pregnancy outcome.[4,5] However, we are unaware of a systematic review analyzing whether this is solely due to the treatment of CIN or also partly due to an association of an underlying communal disorder resulting in both CIN and PTB, thus potentially confounding the association between cervical surgery and PTB. We therefore included a subgroup analysis comparing the risk of PTB for women with untreated CIN compared to healthy women. In

addition, to estimate whether timing of the procedure may affect the risk of PTB before 37 weeks of gestational age, we compared women treated for CIN *during* pregnancy to women with untreated CIN. Another strength of this systematic review is the comprehensive literature search we performed without language restrictions. Furthermore the studies included in this systematic review originated from different countries, making the results more generalizable.

There are several limitations to consider. First, there was heterogeneity among the included studies. Although eyeballing showed the heterogeneity to be limited, heterogeneity is considerable when assessed with the Higgens I^2 test.

Second, the included studies did not allow us to distinguish between the type of treatments in the study group and between CIN I, II and III lesions. In the majority of the studies the severity of dysplasia was not reported. [14, 15, 19, 21, 22, 25, 28, 29]

Finally, some selected studies included women without abnormal histological findings. Bruinsma et al.[16] and Sadler et al.[24] included women referred to a special clinic for CIN, but who ended up having normal histological findings. Both the treated group and the untreated group contained women having normal histological findings. In case of Bruinsma et al. this is respectively 9.5% and 36% and in case of Sadler et al. this is respectively 2.0% and 21.1%.

Interpretation

Several systematic reviews and meta-analysis have been performed on the risk of PTB following different kinds of treatment for CIN. However it remains unclear whether the relationships found are related to cervical surgery, the timing of cervical surgery, to CIN itself or maybe even to an underlying communal disorder resulting both in CIN and PTB, thus potentially confounding the association between cervical surgery and PTB. We did not only compare pregnancy outcomes between women with treated CIN and women without CIN but also compared to women with untreated CIN. In addition, we performed subgroup analyses of women treated for CIN during and before pregnancy.

Previously published systematic reviews and meta-analysis describe a significant association between treatment for CIN and the risk of PTB before 37 weeks of gestation. This is partly in contrast with our results, since we only found a significant increased risk in PTB before 37 weeks of gestation in women treated for CIN *during* pregnancy. However, the data included in the previously published systematic reviews mostly contain women treated for CIN compared to healthy women instead of women with untreated CIN, which leaves the question whether it is the CIN or the treatment that is the cause of the preterm birth.[4, 5, 34, 35] Kyrgiou et al. performed a systematic review and meta-analysis on pregnancy outcomes

after treatment for CIN reported that the risk for PTB among women treated with large loop excision of the transformation zone (LLETZ) or cold knife conisation were 1.7 (95% CI 1.2-2.4) and 2.6 (95% CI 1.8-3.7) times higher respectively than for women without a previous conservative intervention on the cervix. It is not clear whether these women were diagnosed with CIN [34] However, when compared to healthy women; it remains unclear whether it is the treatment or the underlying disease that increases the risk of PTB.

In 2011 a review on the risk of PTB following treatment for precancerous changes in the cervix was published. [35] The authors reported three studies investigating the risk of PTB associated with treatment for CIN compared with women who were diagnosed with CIN but did not receive treatment. These three studies were included in the present meta-analysis.[17, 24, 26] Bruinsma et al. stated that the excisional treatment confers an additional small, but clinically significant risk.[35]

Recently, Conner et al. reviewed the literature on Loop Electrosurgical Excision Procedure (LEEP) and the risk of PTB. [5] They also assessed CIN and the subsequent risks. They found that LEEP was associated with an increased risk of PTB before 37 weeks (RR1.6, 95%CI 1.4-1.9). On the other hand, they concluded that women with a history of LEEP have a similar risk of PTB when compared with women with prior dysplasia but no cervical excision based on four studies, which were included in this meta-analysis.[15,18,24,28] Our analysis, which included an additional 11 studies resulted in a significant higher risk of PTB in the treated group compared to women with CIN lesions but without treatment, which was mainly attributed to treatment for CIN *during* pregnancy. Conner et al. did not mention whether LEEP was performed before or during pregnancy.

Dysfunction of the cervix, especially during pregnancy, is a logical consequence of removal or destruction of a part of the cervix.[34] The pathophysiological mechanism is possibly based on a shortening and weakening of the cervix because of the loss of tissue.[22, 34] The cervical canal is of great importance to develop a mucous plug in pregnancy. The high levels of immunoglobulin and phagocytic cells protect mother and fetus against microorganisms. [36] Potentially cervical surgery might lead to an inability of developing a sufficient mucous plug and therefore the risk of (P)PROM may increase. [22]

Several studies analysed the interval from cervical surgery to pregnancy outcomes and the risk of PTB. The studies are inconclusive whether a shorter time interval increases the risk of PTB. [37] We found a 6-fold increased risk of PTB in women *treated during* pregnancy compared to women with untreated CIN. This result indicates that treatment of CIN *during* pregnancy should be avoided. During pregnancy, the cervix is congested and hyperaemic and one could imagine that the

cervical damage performed in this phase is of more impact. [38-40] In addition, there is less time to rebuild a sufficient cervix. Another argument to refrain from treatment for CIN *during* pregnancy is the higher the risk of intractable bleeding.[38-40]

In screening programs, women with abnormal cervical smears undergo subsequent colposcopy, and, when CIN is diagnosed, women will usually be treated with LLETZ. We have found an increased risk of PTB after treatment for CIN *during* pregnancy. Many preinvasive lesions would never progress to invasive cancer and normalize without intervention. Thus the risk of PTB should be weighed against the risk of these women developing cervical cancer. [42] The age at which screening starts will also affect the number of women who are exposed to the risk of PTB due to treatment for CIN. When screening starts early more women will be treated before they complete their family. One could, when possible based on the findings of cervical screening and a women's risk profile, consider less invasive treatment then the standard regime. Especially when a woman is diagnosed with CIN during pregnancy one should consider expectant management.

We questioned whether the CIN itself or an underlying communal disorder can lead to adverse pregnancy outcomes. Zuo et al. found a significant correlation between the presence of high-risk human papillomavirus and PTB, which could imply that this also applies to women with CIN. Others report that CIN does not lead to a premature delivery. [30, 33, 40] According to Zuo et al and Goldenberg et al. the mechanism for the onset of PTB is the HPV-infection, which triggers the decidua and the foetal membranes to produce cytokines that stimulate prostaglandin synthesis and release, causing uterine contraction, which leads to *spontaneous* PTB. [33, 41] Since previous studies suggested that there is an increased risk of PTB after treatment for CIN when compared with mostly healthy women, and since we did not find a significant difference between women treated for CIN and untreated women, we might consider CIN as a potential risk factor for PTB. Our results suggest that there is no significant difference in women treated for CIN and women with untreated CIN regarding to *spontaneous* PTB. From which we can conclude that the increased risk in PTB before 37 weeks we found, is due to iatrogenic PTB and might be caused by an underlying communal disease. Factors predispose to developing CIN, such as smoking and multiple sexual partners, possibly lead to an increased risk of pregnancy complications.[43]

CONCLUSION

We tried to analyse whether the increased risk of PTB are related to cervical surgery, timing of this procedure, to the presence of CIN in general or maybe even to an underlying communal disorder resulting both in CIN and PTB, thus potentially confounding the association between cervical surgery and PTB. Our meta-analysis shows that the attributed risk of PTB in women who were treated for CIN seems to be due to cervical surgery *during* pregnancy. In case of treatment for CIN *before* pregnancy compared to women with untreated CIN, we did find an increased risk in PTB before 37 weeks of gestation, although insignificant. This means that the circumstances, which lead to the developing of CIN, rather more than CIN itself, are probably involved in the cause of PTB. The risk of (P)PROM was increased in women treated for CIN compared to women with untreated CIN. Our results indicate that there is an increased risk in PTB in women treated for CIN *during* pregnancy and that the increased risk of PTB in women treated for CIN might be caused by an underlying communal disorder for developing CIN and causing iatrogenic PTB.
Additional research is needed to analyse the causal relation of iatrogenic PTB and CIN lesions and treatment and to evaluate the impact of cervical cancer screening programs on PTB.

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