

Original Article

The effects of excisional procedures of the uterine cervix on outcomes of pregnancy: a meta-analysis

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Abstract: This meta-analysis aims to assess the effects of excisional procedures of the uterine cervix on outcomes of following pregnancies. Study design: PubMed, Embase, Medline, Web of Knowledge and the Cochrane trial register were searched with English language restriction for only human beings up to Aug 2015. Data were collected and analyzed by Review manager 5.3. Results: Twenty-four studies were included in this meta-analysis. Women with previous excisional procedures of the uterine cervix had higher risk of preterm delivery, preterm premature rupture of the membranes (PROM) and higher rate of babies with low birth weight. The mean gestational age and the mean birth weight were both lower in excisional procedures of the uterine cervix group. But the perinatal mortality and cesarean section rate were similar in two groups. The preterm rate had no difference between groups with different conization-to-pregnancy interval. The PROM rate and preterm rate were same in loop electrosurgical excision procedure (LEEP) group and in cold knife cone (CKC) group. Conclusions: Previous excisional procedures of the uterine cervix was associated with an increased risk of subsequent preterm delivery, PROM, low birth weight and other unpleasant pregnancy outcomes. And this effect will not decrease with longer conization-to-pregnancy interval. Both LEEP and CKC have the same effect. So the excisional procedures of uterine cervix should be considered carefully, especially to women with a desire for future pregnancy.

Keywords: Pregnancy outcome, excisional procedures of the uterine cervix, cervical conization, loop electrosurgical excision procedure (LEEP), cold knife cone (CKC)

Introduction

The number of women with newly diagnosed cervical cancer largely increases annually, the mean age of women with cervical cancer at diagnosis is increased from 42 years old in 2003 to 46 years old since 2011 in China, both in reproductive period, and women with precancerous or cancerous cells in the cervix can be detected by screening test before developing cervical cancer [1]. Cervical intraepithelial neoplasia (CIN) is most frequently in young women in reproductive age, and a peak incidence occurs among women in their twenties [2]. There is a 5-12% chance of progression to squamous cell cancer, so management guidelines recommend aggressive treatment for women with moderate-to-severe dysplasia [3]. Cold knife conization (CKC), loop electrosurgical excision procedure (LEEP), laser ablation

and laser conization are common conservative methods of treatment to remove the transformation zone and preserve the cervical function.

Treatment for CIN is common among women of reproductive age, and many of them have not completed childbearing yet, does treatment have potentially significant reproductive consequences? But the current body of literatures concerning excisional procedures of the uterine cervix and its effects on subsequent pregnancy outcomes is conflicting [4]. The effect of excisional procedures of the uterine cervix on future pregnancy outcomes is still a controversial issue and more investigations are needed. We performed this Meta analysis and try to determine the effects of excisional procedures of the uterine cervix on future pregnancy outcomes and provide reasonable treatment recommen-

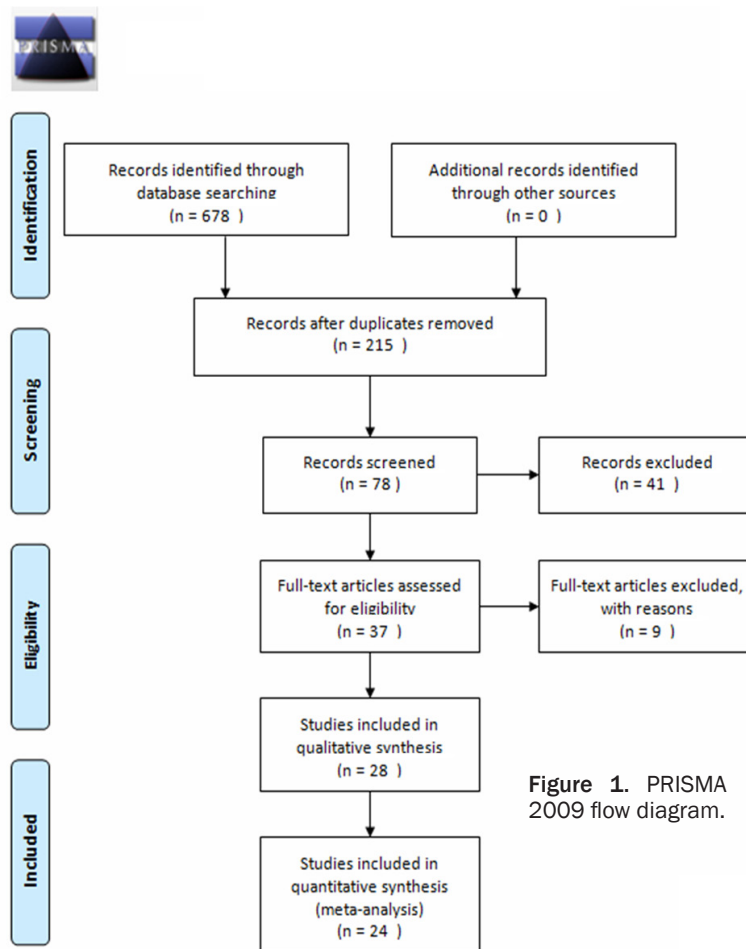


Figure 1. PRISMA 2009 flow diagram.

lished in English. (3) Clear data can be extracted from full test of each study and gathered to analysis. (4) Studies without control groups or without standard deviation were excluded.

Data collection and analysis

Data were collected and analyzed by Review Manager 5.3. Considered outcomes were preterm delivery (<37/32 weeks), low birth weight (<2,500 g), preterm spontaneous rupture of membranes (PROM), perinatal mortality, mean gestational age, mean birth weight, and cesarean section rate. The odds ratio of dichotomous variables and standard means difference of continuous variables were analyzed. 95% confidence interval (95% CI) was given for all effect sizes. The level of significance was set at $P < 0.05$. Fixed effect model was used when $I^2 < 50\%$, otherwise, random effect model was used for analysis.

dations for women with cervical abnormalities and a desire for future fertility.

Materials and methods

Search methods

The following electronic databases were searched up to Aug 2015: PubMed, Embase, Medline, Web of Knowledge and the Cochrane trial register. Search terms included “pregnancy” and “cervical conization” or “excisional procedures of the uterine cervix” or “loop electrosurgical excision procedure (LEEP)” or “cold knife cone (CKC)”, and researches were limited to only human beings. All articles that could possibly be related were preselected. This is a Meta analysis and exempt from Institutional Review Board (IRB) approval.

Selection and exclusion criteria

(1) Studies included must have similar study method. (2) Studies included must be pub-

Results

A total of 24 studies were eligible for our meta-analysis [5-28], and the PRISMA 2009 Flow Diagram shown as **Figure 1**. The characteristics of studies included are shown as **Table 1**. The review authors' judgments about each risk of bias item presented as percentages across all included studies is shown as **Figure 2**.

Women with previous excisional procedures of the uterine cervix had higher risk of preterm delivery (<32 weeks and <37 weeks), shown as **Figure 3** (<32 weeks, 5 studies [5-9], 110/4280 cases of excisional procedures of the uterine cervix group and 533/76550 cases of controls, $P = 0.001$) and **Figure 4** (<37 weeks, 16 studies [5-20], 1897/19459 cases of excisional procedures of the uterine cervix group and 68949/1049566 cases of controls, $P < 0.0001$).

There were 6 studies [6-7, 9, 18, 20, 21] compared the rate of PROM between excisional procedures of the uterine cervix group (297/5106)

Table 1. Characteristics of studies included

	Study group (n)	Control group (n)	Type of studies
Andía D 2011 [5]	189	189	Retrospective case-control multicenter study
Bruinsma F 2007 [6]	1951	2294	Retrospective cohort design
Ortoft G 2010 [7]	721+37	74552	Population-based cohort study
Sadler L 2004 [8]	652	426	Retrospective cohort study
Sjoberg KD 2007 [9]	742	742	Multi-centre, retrospective, case-control study
Acharya G 2005 [10]	45	90	Matched cohort study
Frega A 2013 [11]	475	441	Case-control study
Frey HA 2013 [12]	598	588	Secondary analysis of a multicenter retrospective cohort study
Jakobsson M 2009 [13]	241	17	Retrospective cohort study
Miller ES 2015 [14]	1356	14149	Cohort study
Noehr B 2009 [15]	8180	544498	Population-based data
Nøhr B 2007 [16]	349	14567	Prospective cohort study
Reilly R 2012 [17]	2202	38983	Population-based retrospective cohort study
Shanbhag S 2009 [18]	1103	119216	Retrospective cohort analysis
Tan L 2004 [19]	119	119	Retrospective case control study
Werner CL 2010 [20]	511	240348	Retrospective study
Armarnik S 2011 [21]	53	104617	Population-based study
Paraskevaidis E 2002 [22]	28	28	Case-control study
Ciavattini A 2015 [23]	142	498	Multicenter, retrospective cohort study
	<12 months	≥12 months	
Conner SN 2013 [24]	56	540	Multicenter cohort study
	<12 months	≥12 months	
Liu Y 2014 [25]	124	120	Randomized clinical trial
Mathevet P 2003 [26]	9	9	Randomized trial
Guo HJ 2013 [27]	48LEEP	36CKC	Case control trial
Michelin MA 2009 [28]	95LEEP	102CKC	Case control trial

and controls (23354/540116). The odds ratio was 2.47 and 95% CI was [1.42, 4.31]. Test for overall effect: $Z=3.19$ ($P=0.001$), which meant women with previous c excisional procedures of the uterine cervix had higher risk of PROM, shown as **Figure 5**.

There were 6 studies [5-7, 9, 10, 18] compared the rate of babies with low birth weight (<2500 g) between excisional procedures of the uterine cervix group (508/4810) and controls (10849/195498). The odds ratio was 2.21 and 95% CI was [1.46, 3.35]. Test for overall effect: $Z=3.74$ ($P=0.0002$), which meant women with previous excisional procedures of the uterine cervix had higher rate of babies with low birth weight, shown as **Figure 6**.

The mean gestational age (4 studies [7, 10, 21, 22], 870 cases of excisional procedures of the uterine cervix group and 177702 cases of controls, $P<0.00001$) and the mean birth weight (5 studies [7, 10, 18, 21, 22], 1973 cases of excisional procedures of the uterine cervix group

and 296918 cases of controls, $P<0.00001$) were both lower in excisional procedures of the uterine cervix group, shown as **Figures 7** and **8**.

But the perinatal mortality (6 studies [6, 7, 10, 18, 20, 21], 57 cases of excisional procedures of the uterine cervix group and 6645 cases of controls, $P=0.11$) and cesarean section rate (7 studies [6, 10, 12, 18, 19, 21, 22], 807 cases of excisional procedures of the uterine cervix group and 42160 cases of controls, $P=0.48$) were similar in two groups, shown as **Figures 9** and **10**.

There were 3 studies [17, 23, 24] compared the miscarriage rate between two groups with different time interval from excisional procedures of the uterine cervix to conception (11255 cases <12 months vs. 32548 cases ≥12 months). The odds ratio was 2.15 and 95% CI was [0.81, 5.69]. Test for overall effect: $Z=1.54$ ($P=0.12$), which meant no statistical difference between two groups, shown as **Figure 11**.

Uterine cervix excision and future pregnancy

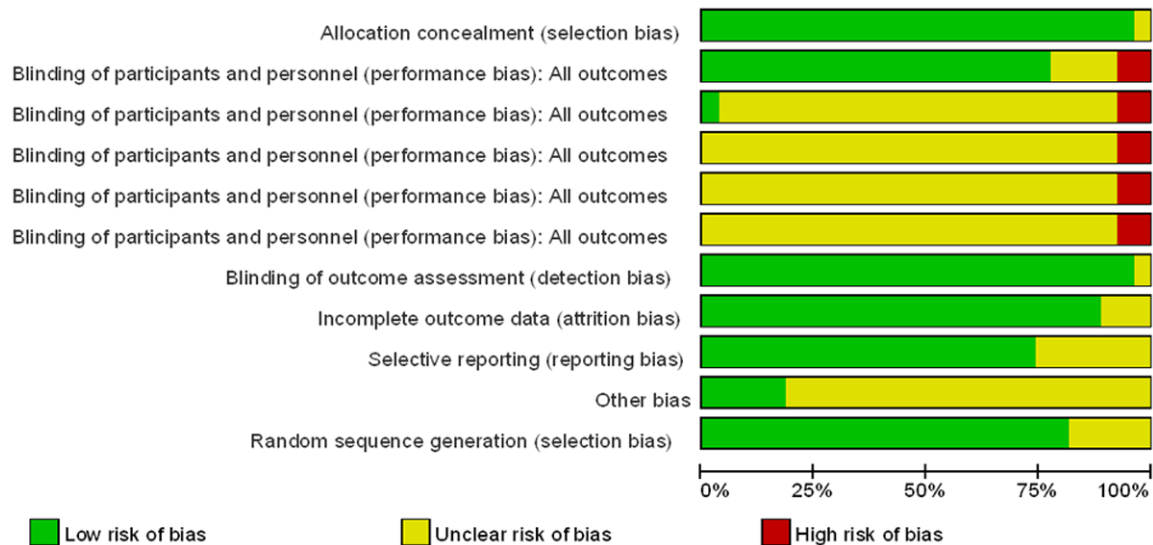


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

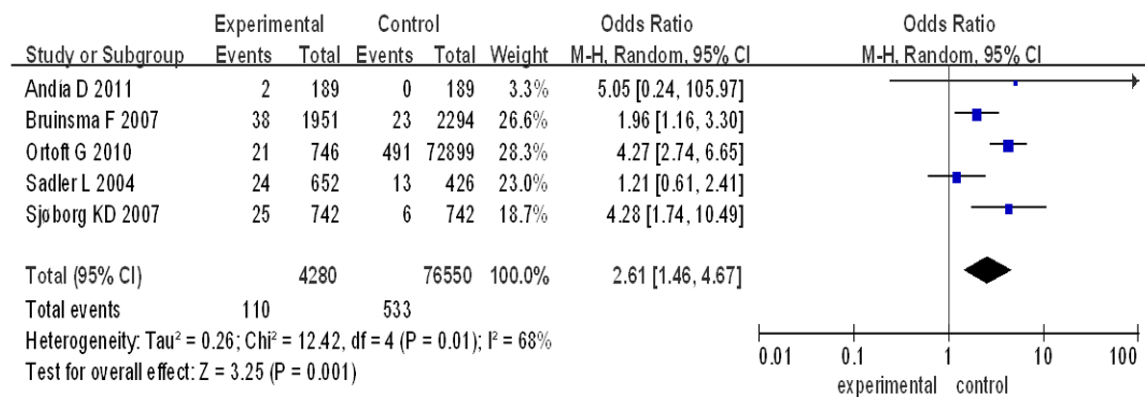


Figure 3. Women with previous cervical conization have higher risk of preterm delivery (<32 weeks).

There were 3 studies [16-17, 24] compared the preterm rate between two groups with different time interval from excisional procedures of the uterine cervix to conception (11203 cases <12 months vs. 32309 cases ≥ 12 months). The odds ratio was 0.93 and 95% CI was [0.85, 1.01]. Test for overall effect: $Z = 1.67$ ($P = 0.10$), which meant no statistical difference between two groups, shown as **Figure 12**.

There were 2 studies [17, 24] compared the preterm rate of two groups with different time interval from excisional procedures of the uterine cervix to conception (5540 cases <6 months vs. 37623 cases ≥ 6 months). The odds ratio was 0.97 and 95% CI was [0.86, 1.09]. Test for overall effect: $Z = 0.47$ ($P = 0.64$), which

meant no statistical difference between two groups, shown as **Figure 13**.

As for the comparing of LEEP and CKC, there were 3 papers [7, 25-26] compared the PROM rate in LEEP group (33/204) and those in CKC group (25/196), and the difference was not statistically significant ($P = 0.59$), shown as **Figure 14**. There were 5 papers [7, 25-28] compared the preterm rate were in LEEP group (42/347) and those in CKC group (62/334), and the difference was not statistically significant either ($P = 0.38$), shown as **Figure 15**.

Discussions

The current body of literatures concerning excisional procedures of the uterine cervix and its

Uterine cervix excision and future pregnancy

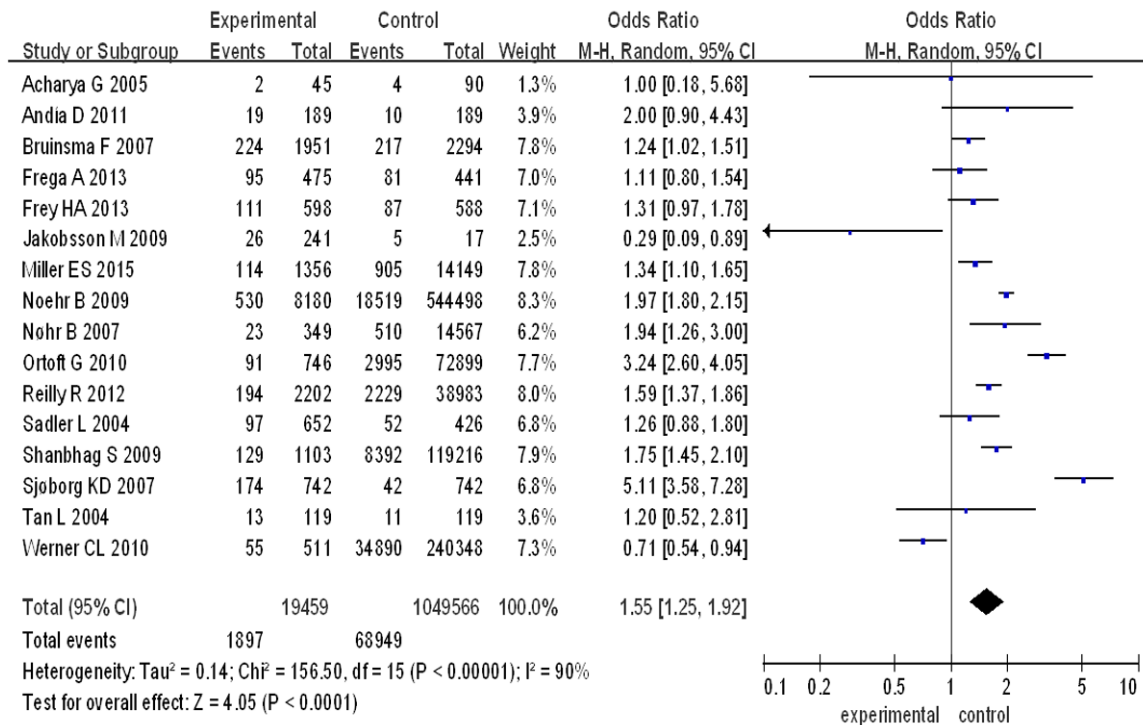


Figure 4. Women with previous cervical conization have higher risk of preterm delivery (<37 weeks).

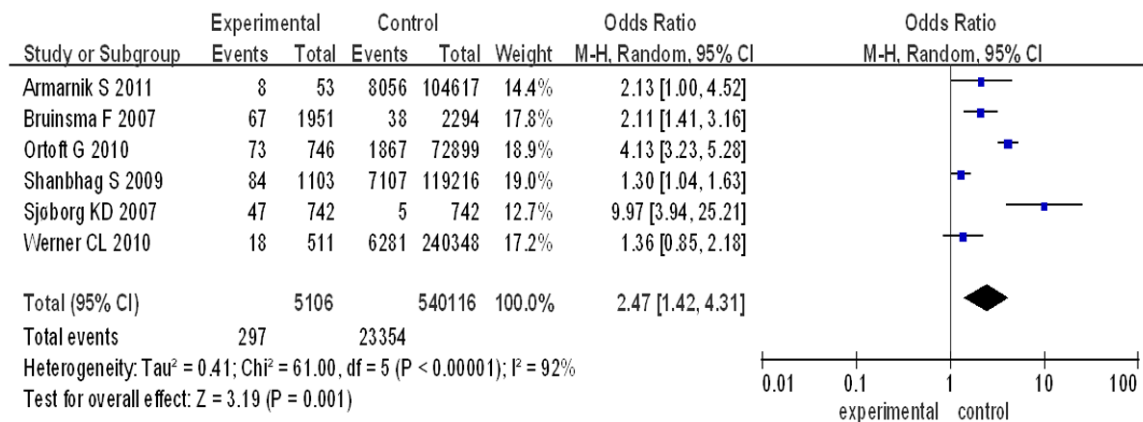


Figure 5. Women with previous cervical conization have higher risk of PROM.

effects on subsequent pregnancy outcomes is conflicting. The results and conclusions vary widely due to the type of conization procedure, the quality of the control group and so on, and more investigations are still needed.

Except those studies analyzed above, there are many more studies discussed the effects of excisional procedures of the uterine cervix on subsequent pregnancy outcomes. Martyn FM's study showed no delay in conception and no

increased risk of problems conceiving in excisional procedures of the uterine cervix group, even when controlling for the volume and depth of tissue removed [29]. But as for the bad effect on future pregnancy outcomes, our meta-analysis showed that women with previous excisional procedures of the uterine cervix had higher risk of preterm delivery (<32 weeks and <37 weeks), preterm premature rupture of the membranes (PROM) and higher rate of babies with low birth weight, the mean gestational age and

Uterine cervix excision and future pregnancy

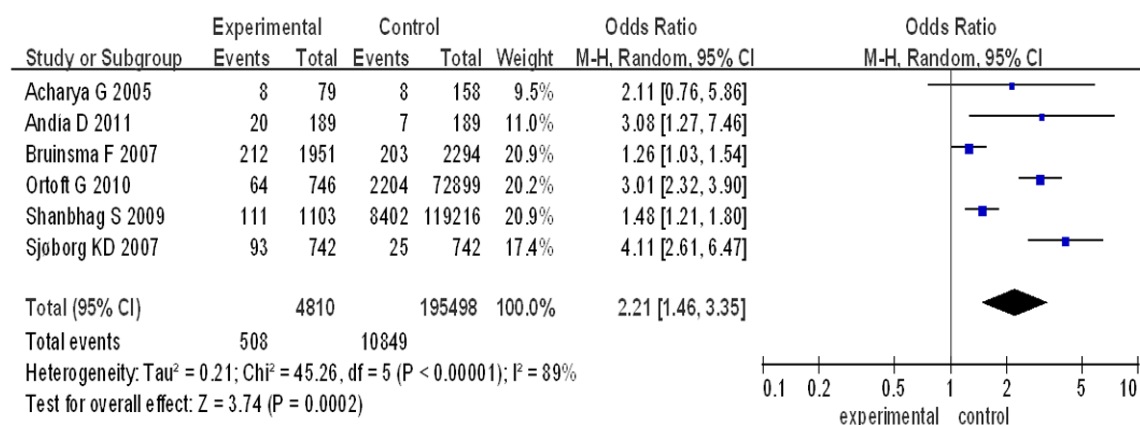


Figure 6. Women with previous cervical conization have higher rate of babies with low birth weight.

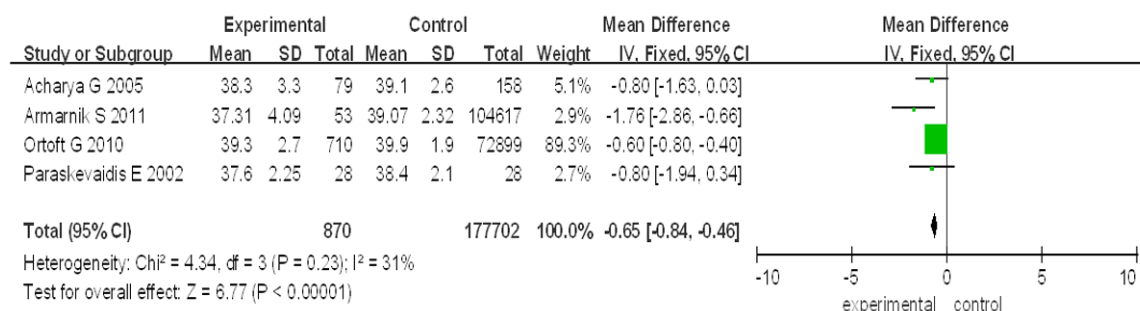


Figure 7. The mean gestational age is lower in cervical conization group.

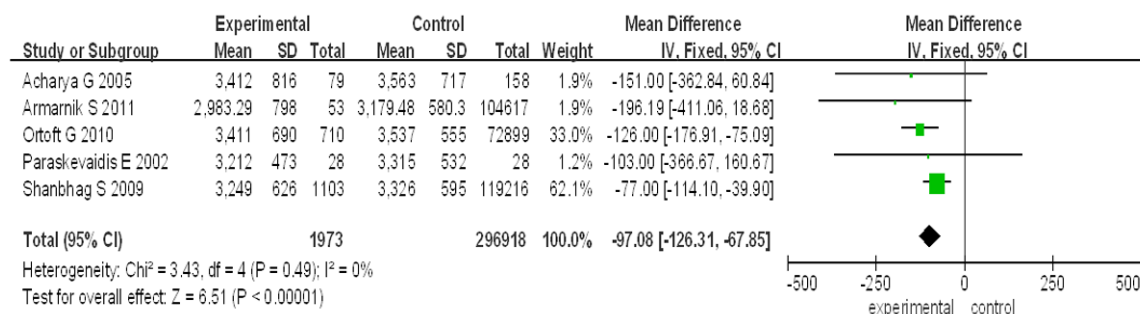


Figure 8. The mean birth weight is lower in cervical conization group.

the mean birth weight were both lower in excisional procedures of the uterine cervix group, which was also supported by other papers [30-33]. We did not conclude the effect of different excisional volume or depth on pregnancy outcomes because of not enough literatures, but there was one study showed that a cervical length of less than 3 cm was significantly increased in LEEP as compared with that of control group, but increasing LEEP volume or depth was not associated with an increased

rate of preterm birth <37 weeks, and LEEP was not associated with a significantly increased risk of perinatal mortality, cesarean section, stillbirth mortality, neonatal mortality, induction, and neonatal intensive care unit admission [33]. The latter result about the risk of perinatal mortality and cesarean section was also supported by our Meta analysis.

Previous study showed that women with a short conization-to-pregnancy interval were at

Uterine cervix excision and future pregnancy

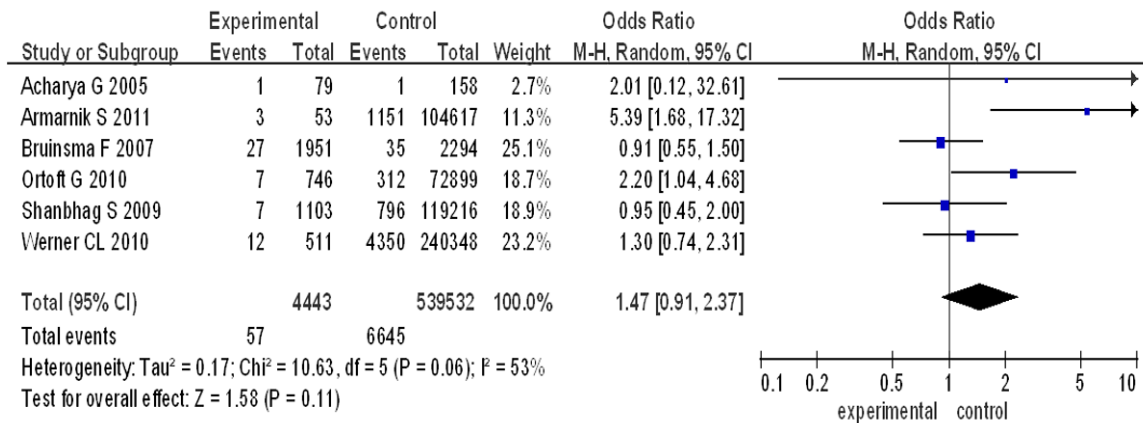


Figure 9. The perinatal mortality is similar in two groups.

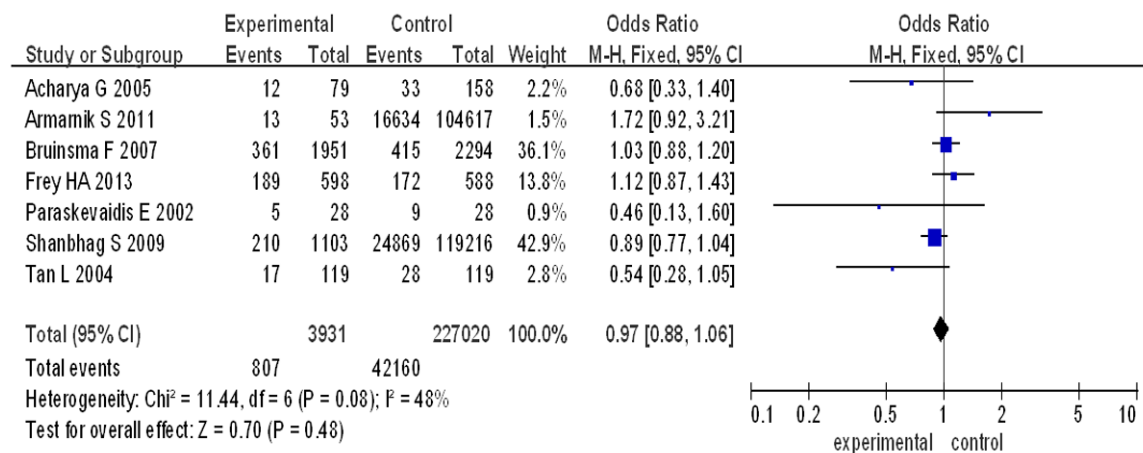


Figure 10. The cesarean section rate is similar in two groups.

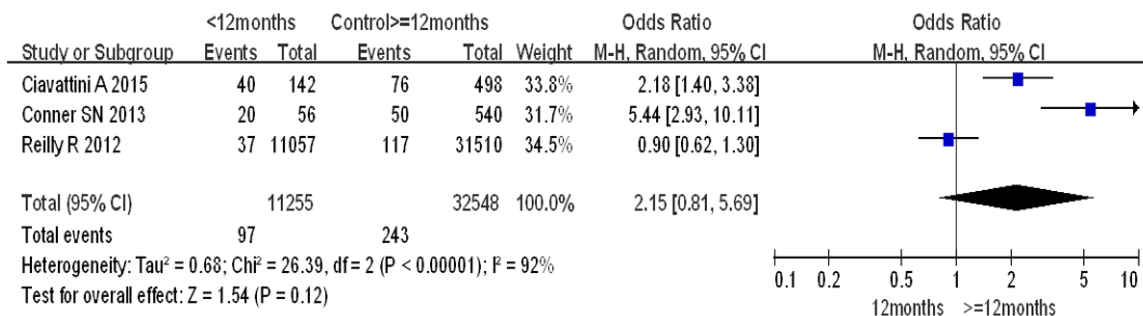


Figure 11. The miscarriage rate has no difference between two groups with different time interval from cervical conization to conception (<12 months vs. ≥ 12 months).

increased risk for preterm birth [34], but this meta analysis found that the preterm rate had no difference between two groups with different time interval from previous excisional pro-

cedures of the uterine cervix to conception (<12 months vs. ≥ 12 months, and <6 months vs. ≥ 6 months). The association between short conization-to-pregnancy interval and preterm

Uterine cervix excision and future pregnancy

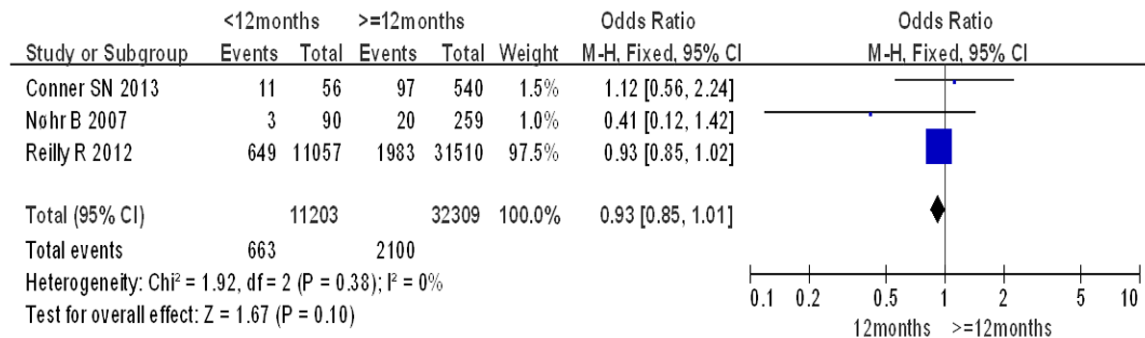


Figure 12. The preterm rate has no difference between two groups with different time interval from cervical conization to conception (<12 months vs. ≥12 months).

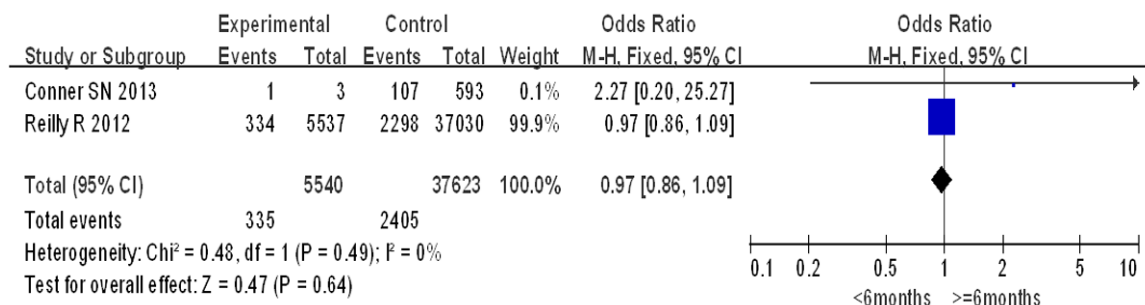


Figure 13. The preterm rate has no difference between two groups with different time interval from cervical conization to conception (<6 months vs. ≥6 months).

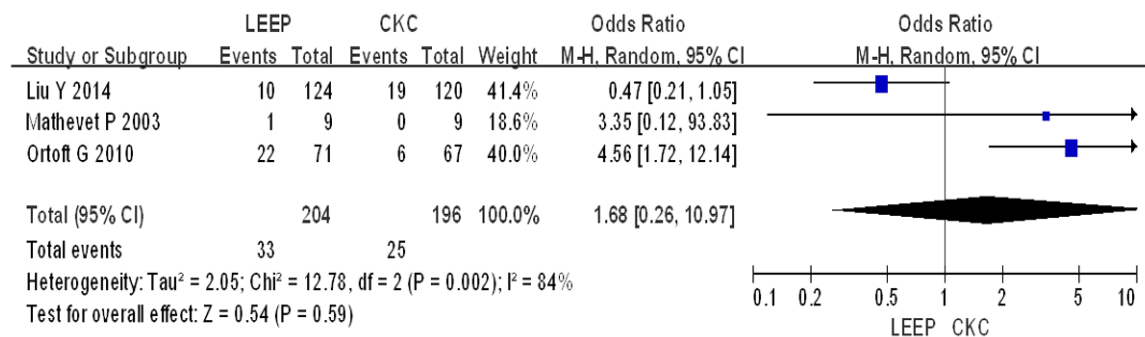


Figure 14. The PROM rate is as same in LEEP group as in CKC group.

birth is still a controversial issue and more investigations are needed.

As for the comparing of LEEP and CKC, one study showed that premature delivery rate was higher in the CKC group than in LEEP group (10/48, 20.83%), the average gestational weeks were shorter in the CKC group (36.9 ± 2.4) than in the LEEP group (38.1 ± 2.4), and suggested that LEEP should be a priority in the

treatment of patients with CIN who want to become pregnant [27]. This idea was also supported by another study, which showed that pregnancies occurred 2.6 and 4.8 years after LEEP and CKC respectively, miscarriages and preterm pregnancies were more frequent in CKC cases versus LEEP, 26% and 5.2%, 23% and 5.5%, respectively [28]. But this Meta analysis collected both two studies and another study, and failed to find statistical difference of

Uterine cervix excision and future pregnancy

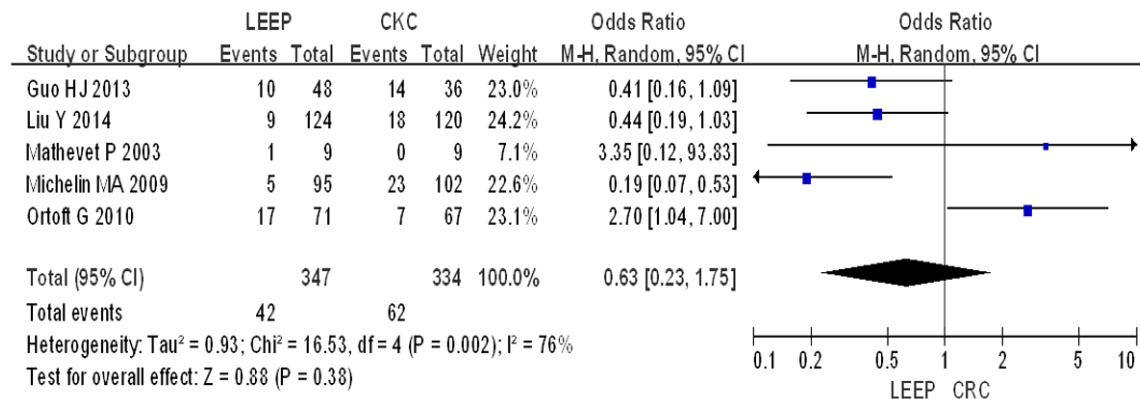


Figure 15. The preterm rate is as same in LEEP group as in CKC group.

PROM rate or preterm rate between LEEP group and CKC group. Is LEEP better than CKC if patients express a desire for pregnancy? We prefer this is also a controversial issue and more investigations are still needed.

The clinical application of excisional procedures of the uterine cervix is more and more widely. The combination of excisional procedures of the uterine cervix and laparoscopic pelvic lymphadenectomy even is feasible as a fertility-sparing surgical approach in selected and informed patients (early-stage cervical cancer, International Federation of Gynecology and Obstetrics stage IA2-IB1, age ≤ 45 years, tumor ≤ 20 mm) [35]. It is necessary to further assess the effect of excisional procedures of the uterine cervix on outcome of following pregnancies.

There are some limitations to this study that should be considered. The number of patients was relatively small in some comparisons. And the heterogeneity of the studies included also affects the credibility of this analysis.

Conclusion

In summary, previous excisional procedures of the uterine cervix is associated with an increased risk of subsequent preterm delivery, PROM, low birth weight and other unpleasant pregnancy outcomes. And this effect will not decrease with longer conization-to-pregnancy interval. Both LEEP and CKC have almost the same effect. So we suggest that excisional procedures of the uterine cervix should be considered carefully, especially to women with a desire for future pregnancy.

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Disclosure of conflict of interest

None.

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Uterine cervix excision and future pregnancy

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