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Vaginal Progesterone is as Effective as Cervical Cerclage to Prevent Preterm Birth in Women with a Singleton Gestation, Previous Spontaneous Preterm Birth and a Short Cervix: Updated Indirect Comparison Meta-Analysis

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VAGINAL PROGESTERONE IS AS EFFECTIVE AS CERVICAL CERCLAGE TO PREVENT PRETERM BIRTH IN WOMEN WITH A SINGLETON GESTATION, PREVIOUS SPONTANEOUS PRETERM BIRTH AND A SHORT CERVIX: UPDATED INDIRECT COMPARISON META-ANALYSIS

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Condensation

Vaginal progesterone and cerclage are equally effective for preventing preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a sonographic short cervix

Short title of the paper: Vaginal progesterone versus cerclage in women with a singleton gestation, previous spontaneous preterm birth and a short cervix

Implications and Contributions

A. To compare the efficacy of vaginal progesterone and cerclage in preventing preterm birth and adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth and a midtrimester sonographic short cervix

B. Both vaginal progesterone and cerclage were associated with a significant reduction in the risk of preterm birth <35 and <32 weeks of gestation and composite perinatal morbidity/mortality compared with placebo/no cerclage. Adjusted indirect comparison meta-analyses showed no statistically significant differences between vaginal progesterone and cerclage in preventing preterm birth <35 and <32 weeks of gestation, and composite perinatal morbidity/mortality

C. This updated meta-analysis reaffirms that vaginal progesterone and cerclage are equally effective in preventing preterm birth and improving perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth, and a sonographic short cervix.

ABSTRACT

BACKGROUND: An indirect comparison meta-analysis published in 2013 reported that both vaginal progesterone and cerclage are equally efficacious for preventing preterm birth and adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth and a sonographic short cervix. The efficacy of vaginal progesterone has been disputed after publication of the OPPTIMUM study.

OBJECTIVE: To compare the efficacy of vaginal progesterone and cerclage in preventing preterm birth and adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth and a midtrimester sonographic short cervix.

DATA SOURCES: MEDLINE, EMBASE, LILACS, and CINAHL (from their inception to March 2018); Cochrane databases, bibliographies, and conference proceedings.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials comparing vaginal progesterone with placebo/no treatment or cerclage with no cerclage in women with a singleton gestation, previous spontaneous preterm birth and a sonographic cervical length <25 mm.

STUDY APPRAISAL AND SYNTHESIS METHODS: Updated systematic review and adjusted indirect comparison meta-analysis of vaginal progesterone versus cerclage using placebo/no cerclage as the common comparator. The primary outcomes were preterm birth <35 weeks of gestation and perinatal mortality. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

RESULTS: Five trials comparing vaginal progesterone versus placebo (265

women) and 5 comparing cerclage versus no cerclage (504 women) were included. Vaginal progesterone, compared with placebo, significantly reduced the risk of preterm birth <35 and <32 weeks of gestation, composite perinatal morbidity/mortality, neonatal sepsis, composite neonatal morbidity, and admission to the neonatal intensive care unit (RRs from 0.29-0.68). Cerclage, compared with no cerclage, significantly decreased the risk of preterm birth <35, <37, <32, and <28 weeks of gestation, composite perinatal morbidity/mortality, and birthweigth <1500 g (RRs from 0.64-0.70). Adjusted indirect comparison meta-analyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes.

CONCLUSIONS: Vaginal progesterone and cerclage are equally effective for preventing preterm birth and improving perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth, and a midtrimester sonographic short cervix. The choice of treatment will depend on adverse events and cost-effectiveness of interventions, and patient/physician's preferences.

Key words: prematurity; recurrent preterm birth; uterine cervix; cervical length; transvaginal ultrasound; perinatal mortality; admission to neonatal intensive care unit; birth weight <1500 g; progestin; progestogens; cervical stitch

INTRODUCTION

Worldwide, an estimated 11.1% of all livebirths in 2010 were born preterm (14.9 million babies).[1] In the United States, the preterm birth rate had declined steadily from 2007 to 2014. In 2016, the rate of preterm birth rose to 9.85%, a 2% rise from 2015 and the second straight year of increase for this rate.[2] Complications of preterm birth are the leading cause of neonatal mortality, responsible for 35% of the world's 2.6 million deaths that occurred in 2016.[3] In addition to its contribution to neonatal and child morbidity and mortality, preterm birth has lifelong effects on neurodevelopmental functioning such as increased risk of cerebral palsy, intellectual disability, visual and hearing impairments, and an increased risk of chronic disease in adulthood.[4-11]

It is widely accepted that preterm birth is a syndrome caused by several pathological processes such as infection, vascular and decidual disorders, uterine overdistension, breakdown of maternal-fetal tolerance, a decline in progesterone action, and cervical disease.[12-14] A previous spontaneous preterm birth is a well-known risk factor for recurrent spontaneous preterm birth.[15-27] A recent meta-analysis reported that the overall risk of recurrent spontaneous preterm birth <37 weeks of gestation was 30%.[28] A short cervix, conventionally defined as a transvaginal sonographic cervical length ≤25mm in the midtrimester of pregnancy, is also an important risk factor for this condition and has emerged as one of the strongest and most consistent predictors of preterm birth in asymptomatic women with a singleton or twin gestation.[29-67] The combination of previous spontaneous preterm birth and a short cervix markedly increases the risk of recurrent spontaneous preterm birth. Indeed, among women with a

previous spontaneous preterm birth, the risk of recurrent spontaneous preterm birth is about 3-fold higher in those with a cervical length ≤25 mm than in those with a cervical length >25 mm in the midtrimester.[68,69]

Vaginal progesterone administration[70-81] and the placement of a cervical cerclage[71,75,82-88] have been proposed for preventing preterm birth in patients with a singleton gestation, previous spontaneous preterm birth, and a sonographic short cervix. In 2011, an individual patient data (IPD) meta-analysis evaluated the efficacy of cerclage for the prevention of preterm birth and perinatal morbidity and mortality in asymptomatic women with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm before 24 weeks of gestation.[82] Cerclage, compared with no cerclage, significantly decreased the risk of preterm birth <37, <35, <32, and <28 weeks of gestation, composite perinatal morbidity and mortality, and birthweight <1500 g. In 2013, another IPD meta-analysis reported that vaginal progesterone administration to women with the same characteristics was associated with a significant reduction in the risk of preterm birth <32 weeks of gestation, composite perinatal morbidity and mortality, composite neonatal morbidity, and admission to the neonatal intensive care unit (NICU).[71] Data from these 2 IPD meta-analyses were used for performing an adjusted indirect comparison meta-analysis of vaginal progesterone versus cerclage using placebo/no cerclage as the common comparator.[71] This indirect meta-analysis did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth and a midtrimester cervical length <25 mm.[71] It was concluded that both

interventions are equally efficacious for preventing preterm birth and adverse perinatal outcomes in these patients.

To date, only two small randomized controlled trials have directly compared vaginal progesterone and cerclage in women with these characteristics.[89,90] However, the trials lacked power to detect group differences. In 2016, the OPPTIMUM study, which tested the effect of vaginal progesterone in women at risk for preterm birth, reported that vaginal progesterone did not reduce the risk of preterm birth or neonatal morbidity and mortality in the entire population, or in the subgroup of women with a cervical length ≤25 mm.[91] Therefore, it is necessary to reassess the efficacy of vaginal progesterone in women with a singleton gestation, previous spontaneous preterm birth and a midtrimester sonographic short cervix, and to update the adjusted indirect comparison meta-analysis of vaginal progesterone versus cerclage in patients with these characteristics. Adjusted indirect comparisons offer a unique opportunity to compare competing interventions. Their results usually, but not always, agree with the results of head-to-head randomized controlled trials.[92-98] When direct evidence from randomized controlled trials is lacking or insufficient, the adjusted indirect comparison meta-analysis may provide useful information on the relative efficacy of the competing interventions.

The aim of this study was to compare the efficacy of vaginal progesterone and cerclage in preventing preterm birth and adverse perinatal outcomes in women with a singleton gestation, previous spontaneous preterm birth and a midtrimester sonographic short cervix by using adjusted indirect comparison meta-analytic techniques.

MATERIALS AND METHODS

This updated indirect comparison meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[99] and suggested guidelines for IPD[100] and indirect meta-analyses.[101] To ensure consistency, we used the same methodology as in our previous study.[71] The study protocol was prospectively registered with the PROSPERO database of systematic reviews (CRD42017077311). Two of the authors (AC-A and RR) independently retrieved and reviewed studies for eligibility, assessed their risk of bias, and extracted data. All disagreements encountered in the review process were resolved through consensus.

Literature search and study selection

In our previous indirect comparison meta-analysis,[71] MEDLINE, EMBASE, CINAHL, LILACS, the Cochrane Central Register of Controlled Trials, and Research Registers of ongoing trials were searched from the inception of each database to October 31, 2012. An updated literature search was undertaken in these databases from November 1, 2012 to March 20, 2018 using a combination of keywords and text words related to progesterone, cervical cerclage, and preterm birth to identify randomized controlled trials comparing vaginal progesterone versus placebo/no treatment, or cerclage versus no cerclage for the prevention of preterm birth in women with singleton gestations. Google Scholar, proceedings of congresses/meetings on maternal-fetal medicine, reference lists of identified studies, and review articles were also searched. There were no language restrictions. Trials were eligible if the primary aim of the study was to prevent preterm birth in asymptomatic women with a singleton gestation, previous

spontaneous preterm birth and a sonographic short cervix (cervical length <25 mm) in the midtrimester, or to prevent preterm birth in women with other characteristics but for whom outcomes were available in those with a singleton gestation, previous spontaneous preterm birth, and a pre-randomization cervical length <25 mm. Trials were excluded if they (1) were quasi-randomized, (2) assessed vaginal progesterone in women with threatened or arrested preterm labor, second trimester bleeding or premature rupture of membranes, (3) evaluated vaginal progesterone administration in the first trimester to prevent miscarriage, (4) assessed history-indicated cerclage (placed for the sole indication of poor obstetric history), physical examination-indicated cerclage (placed for second-trimester cervical dilatation), or compared different cerclage techniques or outpatient cerclage versus inpatient cerclage, or (5) did not provide data for women with a singleton gestation, previous spontaneous preterm birth, and cervical length <25 mm in the midtrimester.

Data collection and extraction

For the IPD meta-analysis that compared vaginal progesterone versus placebo, we contacted the principal investigators of eligible trials to request access to the data. Authors were supplied with a data extraction sheet and requested to supply anonymized data about baseline characteristics, interventions and outcomes for each randomized patient in the trial. Data provided by the investigators were systematically checked for completeness, duplication, consistency, feasibility, and integrity of randomization. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary. Finally, data on participant characteristics and outcomes were extracted for women with a singleton

gestation, previous spontaneous preterm birth and a cervical length <25 mm, and were uploaded to the main study database. We also extracted data from each study on its characteristics and details of interventions. For studies comparing cerclage versus no cerclage, data on proportions and relative risks (RRs) with 95% confidence intervals (CIs) for each outcome measure were extracted from the IPD meta-analysis by Berghella et al,[82] which used a similar approach to that described above.

Outcome measures

The prespecified primary outcomes were preterm birth <35 weeks of gestation and perinatal mortality. Secondary outcomes were preterm birth <37, <32, and <28 weeks of gestation, respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, composite neonatal morbidity (defined as the occurrence of any of the above mentioned neonatal morbidities), composite perinatal morbidity and mortality (defined as the occurrence of any of the above mentioned neonatal morbidities or perinatal death), admission to the neonatal intensive care unit (NICU), and birthweight <2500 g and <1500 g.

Risk of bias Assessment

Assessments of risk of bias for included trials were done according to the seven domains outlined in the Cochrane Handbook for Systematic Reviews of Interventions (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).[102] This tool categorizes studies by low, unclear, or high risk of bias in each domain.

Statistical analysis

For studies comparing vaginal progesterone versus placebo, we performed an IPD meta-analysis using a two-stage approach. In the first stage, estimates of effect were derived from the IPD for each trial, and in the second stage, these were combined using standard methods for meta-analyses of aggregate data to give a pooled RR with 95% CI.[103] A similar approach was used in the IPD meta-analysis of trials that evaluated cerclage versus no cerclage.[82] Heterogeneity of the results among studies was tested with the quantity I^2 in the IPD meta-analysis of vaginal progesterone versus placebo[104] and the Mantel-Haenszel Q statistics in the IPD meta-analysis of cerclage versus no cerclage. Results from individual studies were pooled using a fixed-effects model if substantial statistical heterogeneity was not present (I^2 ≤30% or P ≥0.10 for Mantel-Haenszel Q statistics). Otherwise, random-effects models were used to pool data across studies.

Number needed to treat (NNT) with 95% CI was calculated where meta-analysis of dichotomous outcomes revealed a statistically significant beneficial or harmful effect of vaginal progesterone or cerclage.[105] We also planned to explore potential sources of heterogeneity and to assess publication and related biases if at least ten studies were included in a meta-analysis but these analyses were not undertaken due to the limited number of trials included in the review.

The adjusted indirect comparison meta-analysis of vaginal progesterone versus cerclage was performed according to the Bucher's method.[106] In this approach, the direct comparisons A versus B and C versus B with the common comparator link B are used to yield an indirect comparison of A versus C. As vaginal progesterone and cerclage have been compared to placebo and no

cerclage, respectively, indirect comparison was enabled by the "common" placebo/no cerclage arms. An extension of the Bucher's method was used to convert the summary estimates (lnRRs) and measures of uncertainty (variances) from the two meta-analyses into a RR (95% CI) that represented the difference between vaginal progesterone and cerclage. This method is well validated and recommended as the preferred method for indirect comparison, superior to other methods, as it preserves the randomization and retains the methodological properties of the randomized controlled trials.[92,94,96,107]

We carried out a subgroup analysis (direct and adjusted indirect comparisons) for women with a cervical length <16 mm. Moreover, we performed a sensitivity analysis (direct and adjusted indirect comparisons) to explore the impact of co-interventions on the direction and size of effect for preterm birth and perinatal mortality. In this sensitivity analysis, we excluded women who received 17α-hydroxyprogesterone caproate (17-OHPC) or vaginal progesterone in trials that compared cerclage versus no cerclage and women who received a cerclage in studies that compared vaginal progesterone with placebo. This analysis was performed because it is unclear whether the effects of progesterone and cerclage are additive in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix. A prespecified sensitivity analysis to explore the impact of study quality on results was not carried out because all trials were considered as at low risk of bias. Subgroup and sensitivity analyses were performed only for the outcomes measures preterm birth <35 and <32 weeks of gestation, and perinatal mortality.

One author (AC-A) conducted all statistical analyses using Review Manager software (version 5.3.5; Nordic Cochrane Centre, Copenhagen, Denmark) for performing direct meta-analyses and Indirect Treatment Comparison software (version 1.0; Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada) to perform adjusted indirect comparison meta-analyses.

This study was exempted from review by the Human Investigation Committee Administration Office of Wayne State University because all included studies were published previously and had each received local Institutional Review Board approvals and informed consent from participants.

RESULTS

Results of the search

Our previous search yielded 32 potentially relevant studies of which 9 were included (4 comparing vaginal progesterone versus placebo[108-111] and 5 comparing cerclage versus no cerclage[112-116]). The updated search identified 4 randomized controlled trials that compared vaginal progesterone versus placebo[91,117-119] and 1[120] that compared cerclage versus no cerclage in singleton gestations with the aim of preventing preterm birth and/or adverse perinatal outcomes. Three of the four studies that assessed vaginal progesterone versus placebo were excluded because they included women without previous spontaneous preterm birth,[117] or women with a short cervix (cervical length ≤28 mm) who underwent cerclage before randomization,[118] and data on cervical length were not collected before randomization.[119] A trial that assessed cerclage versus no cerclage in singleton gestations with a short cervix (cervical length <25 mm) was excluded because data on 14 women with a previous preterm birth that were included in this study could

not be obtained.[120] Thus, only a new trial (the OPPTIMUM study[91]) was included in this updated indirect comparison meta-analysis. In total, 10 trials met the inclusion criteria which provided data for 769 women with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm at midtrimester.

Characteristics and risk of bias of included studies

Table 1 depicts the main characteristics of the 10 studies included in this indirect comparison meta-analysis. Five double-blind, placebo-controlled trials, including 265 women, compared vaginal progesterone versus placebo.[91,108-111] Two studies evaluated the use of vaginal progesterone in women with a short cervix (cervical length ≤15 mm[108] and cervical length between 10 and 20 mm[111]), one in women with a previous spontaneous preterm birth,[109] one in women with a previous spontaneous preterm birth, uterine malformations or twin gestation,[110] and the remainder in women with a previous spontaneous preterm birth, short cervix (cervical length ≤25 mm), or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth.[91] The daily dose of vaginal progesterone used in the trials varied from 90-200 mg and the treatment was administered from 18-25 to 34-36 weeks of gestation. Thirty women (25 in the study by Norman et al[91] and 5 in the study by Hassan et al[111]) underwent a cerclage after randomization.

Five trials, including 504 women, compared cerclage versus no cerclage in women with a sonographic short cervix.[112-116] Gestational age at cervical length screening varied between 14 and 24 weeks of gestation. Four trials used the McDonald procedure[112,113,115,116] and one used the Shirodkar technique.[114] Rescue cerclage in women allocated to the no cerclage group was allowed in three studies based on physical examination[116] or on ultrasonographic cervical changes.[112,113] In

the trial by Owen et al,[116] 99 women received 17-OHPC and one received vaginal progesterone.[121]

All 10 studies that were included in the meta-analysis had adequate random sequence generation and allocation concealment, were free of selective outcome reporting, and had adequate handling of incomplete outcome data. In the 5 trials that evaluated vaginal progesterone, there was blinding of participants, health care providers and outcome assessors. In the 5 trials that evaluated cerclage, blinding of participants and personnel was not feasible due to the nature of the intervention. It was unclear if outcome assessors were blinded from knowledge of which intervention a participant received. However, we considered that assessment of most outcomes included in our review are objective in nature and thus, were not likely to be influenced by a lack of blinding in studies that evaluated cerclage. All but one study[91] had no obvious risk of other biases. In fact, the study by Norman et al[91] was at high risk of compliance bias because only 66% of patients with a cervical length ≤25 mm had a compliance ≥80%, which can affect the trial's statistical power to detect the effects of intervention.[122] Overall, all 10 trials were considered to be at low risk of bias.

Comparability of the vaginal progesterone and cerclage trials

All women included in this updated indirect comparison meta-analysis (265 from trials that evaluated vaginal progesterone and 504 from trials that evaluated cerclage) had a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm detected in the midtrimester (most at 16-24 weeks of gestation). The percentage of patients with a cervical length <16 mm was 42.6% in the trials that evaluated vaginal progesterone and 30.6% in the trials that evaluated

cerclage. Women included in the trials that evaluated vaginal progesterone had a mean (SD) age and body mass index of 27.0 (6.3) years and 29.4 (6.5) kg/m^2, respectively, and Black and White women represented 75% of the study population. The sociodemographic characteristics of women included in the IPD meta-analysis that evaluated cerclage were not reported in the study publication.[82] However, patient characteristics reported in individual trials of cerclage were comparable to those of patients who participated in trials of vaginal progesterone. For example, in the study by Owen et al,[116] the largest that assessed cerclage, Black and White women represented 75% of the study population and the mean age and body mass index were 26.5 years and 29.6 kg/m^2, respectively. Finally, the rates of most outcome measures in the control groups of trials that evaluated vaginal progesterone and cerclage were similar (Table 2).

Direct comparisons

Vaginal progesterone administration to patients with a singleton gestation, previous spontaneous preterm birth, and a midtrimester cervical length <25 mm significantly reduced the risk of preterm birth <35 weeks (RR 0.68; 95% CI, 0.50-0.93) and <32 weeks of gestation (RR, 0.60; 95% CI, 0.39-0.92), neonatal sepsis (RR, 0.38; 95% CI, 0.15-0.96), composite neonatal morbidity (RR, 0.29; 95% CI, 0.11-0.81), composite perinatal morbidity and mortality (RR, 0.43; 95% CI, 0.20-0.94), and admission to the NICU (RR, 0.46; 95% CI, 0.30-0.70) (Table 2).

The use of cerclage in women with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm in the midtrimester was associated with a significantly lower risk of preterm birth <35 weeks (RR 0.70; 95% CI, 0.55-0.89), <37 weeks (RR 0.70; 95% CI, 0.58-0.83), <32 weeks (RR, 0.66;

95% CI, 0.48-0.91), and <28 weeks of gestation (RR 0.64; 95% CI, 0.43-0.96), composite perinatal morbidity and mortality (RR, 0.64; 95% CI, 0.45-0.91), and birthweight <1500 g (RR, 0.64; 95% CI, 0.45-0.90). NNTs for vaginal progesterone varied from 5-16 (median, 7) and for cerclage from 6-14 (median, 11).

Both, vaginal progesterone and cerclage were associated with a non-significant decrease in the risk of perinatal mortality (RR, 0.63; 95% CI, 0.26-1.56 for vaginal progesterone and RR, 0.65; 95% CI, 0.40-1.07 for cerclage) and respiratory distress syndrome (RR, 0.38; 95% CI, 0.13-1.07 for vaginal progesterone and RR, 0.61, 95% CI, 0.32-1.19 for cerclage). The rates of grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and birthweight <2500 g did not differ significantly between the vaginal progesterone and placebo groups, and between the cerclage and no cerclage groups. There was no substantial heterogeneity in any of the meta-analyses that compared vaginal progesterone versus placebo and cerclage versus no cerclage.

Indirect comparison

Adjusted indirect comparison meta-analyses showed no statistically significant differences between vaginal progesterone and cerclage in preventing preterm birth <35 weeks of gestation (RR, 0.97; 95% CI, 0.66-1.44; *P*=0.93) and perinatal death (RR, 0.97; 95% CI, 0.35-2.69; *P*=0.96) (Table 3). There were no significant differences between vaginal progesterone and cerclage for any of the secondary outcome measures. Estimated RRs ranged from 0.48 for composite neonatal morbidity (favoring vaginal progesterone) to 1.79 for grade III/IV intraventricular hemorrhage (favoring cerclage), but all 95% CIs included 1 with most *P* values >0.75. These results indicate that vaginal progesterone and cerclage are not

significantly different in terms of efficacy for reducing the risk of preterm birth and adverse perinatal outcomes.

Subgroup and sensitivity analyses

Among women with a cervical length <16 mm, both vaginal progesterone and cerclage were associated with a significant reduction in the risk of preterm birth <35 weeks of gestation (Table 4). Moreover, cerclage significantly reduced the rate of preterm birth <32 weeks of gestation these patients. Vaginal progesterone and cerclage significantly decreased the risk of preterm birth <35 and <32 weeks of gestation in a sensitivity analysis that excluded both patients who received progestogens in trials that evaluated cerclage and those in whom a cerclage was placed in trials that evaluated vaginal progesterone. No statistically significant differences were observed in the adjusted indirect comparisons between vaginal progesterone and cerclage in subgroup and sensitivity analyses.

COMMENT

Principal findings of the study

The results of this updated indirect comparison meta-analysis indicate that vaginal progesterone and cerclage are equally efficacious in preventing preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a sonographic short cervix. Indeed, vaginal progesterone significantly decreased the risk of preterm birth <35 and <32 weeks of gestation, neonatal sepsis, composite neonatal morbidity, composite perinatal morbidity and mortality, and admission to NICU as compared with placebo. On the other hand, cerclage was associated with a significant reduction in the risk of preterm birth <37, <35, <32, and <28 weeks of gestation, composite perinatal morbidity and mortality, and birthweight <1500 g

when compared with no cerclage. Both interventions were associated with a non-significant ~36% reduction in the rate of perinatal death. Adjusted indirect comparisons showed that there were no significant differences between the efficacy of vaginal progesterone and cerclage in the prevention of preterm birth or adverse perinatal outcomes. These findings were consistent with sensitivity analyses that excluded patients who received co-interventions. Finally, a subgroup analysis revealed that both interventions significantly reduced the rate of preterm birth <35 weeks of gestation in women with a cervical length <16 mm.

Thus far, only two small randomized controlled trials have directly compared vaginal progesterone and cerclage in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix.[89,90] Ionescu et al[89] performed a randomized controlled trial, reported in abstract form only, in which women with a singleton gestation, previous preterm birth, and a cervical length <25 mm before 24 weeks of gestation were randomly assigned to receive either vaginal progesterone 200 mg/d (N=46) or cerclage (N=46). The mean gestational age at delivery was not significantly different between women allocated to receive vaginal progesterone (31.5 weeks) and those allocated to receive a cerclage (32.9 weeks). Chandiramani et al[90] conducted a randomized controlled trial that compared vaginal progesterone 400 mg/d (N=17) versus cerclage (N=19) in women with a singleton gestation, at least one previous spontaneous preterm birth, and a cervical length <25 mm before 24 weeks of gestation. There was no statistically significant difference in mean gestational at delivery between the vaginal progesterone (31.5 ± 9.0 weeks) and cerclage (33.7 ± 7.7 weeks) groups (*P*=0.23). The authors of these trials provided additional information to a Cochrane review that assessed the

use of cerclage in women with singleton gestations at high risk for preterm birth,[123] which allowed the performance of direct comparison meta-analyses between vaginal progesterone and cerclage in women with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm in the midtrimester. In accordance with the results of our indirect comparison meta-analysis, the Cochrane review reported that there were no significant differences between cerclage and vaginal progesterone in the risk of preterm birth <37 weeks (RR, 1.16; 95% CI, 0.64-2.08), <34 weeks (RR, 1.01; 95% CI, 0.51-2.01), and <28 weeks of gestation (RR, 0.92; 95% CI, 0.37-2.27), perinatal mortality (RR, 0.94; 95% CI, 0.36-2.48), and serious neonatal morbidity (RR, 0.49; 95% CI, 0.05-4.52).[123] However, data from one study[89] showed that the rates of both preterm premature rupture of membranes and use of tocolytic agents were significantly higher in the cerclage group than in the vaginal progesterone group (17% versus 2%; RR, 8.00; 95% CI, 1.04-61.42 for preterm premature rupture of membranes; and 65% versus 17%; RR, 3.75; 95% CI, 1.93-7.29 for use of tocolytic agents). In the absence of adequately powered, high-quality, randomized controlled trials comparing vaginal progesterone and cerclage, our indirect comparison treatment meta-analysis provides the best available evidence regarding comparative efficacy of the two interventions.

Strengths and limitations

The main strengths of our study include: (1) the rigorous methodology used for performing the indirect comparison meta-analysis; (2) the use of individual patient data from direct comparisons of vaginal progesterone versus placebo and cerclage versus no cerclage for performing indirect comparisons of vaginal progesterone

versus cerclage; (3) the low risk of bias for most trials included in the review; (4) the comparability of trial and patients characteristics between studies that evaluated vaginal progesterone and those that evaluated cerclage; (4) the remarkably similar rates of preterm birth and adverse perinatal outcomes found in control groups of trials that evaluated vaginal progesterone and cerclage making more homogeneous the common comparator placebo/no cerclage in indirect meta-analyses; (5) the absence of statistical heterogeneity in all direct meta-analyses performed; (6) the robustness of the study findings to sensitivity analyses restricted to patients who did not receive co-interventions; and (7) the consistency between the results obtained in our indirect comparison meta-analysis and those obtained in the meta-analysis[123] of two trials that directly compared vaginal progesterone and cerclage.

Some potential limitations must also be considered. First, the OPPTIMUM study[91] did not collect data on respiratory distress syndrome, the most common complication of preterm birth, which reduced the sample size of meta-analyses for the composite outcomes of neonatal morbidity and perinatal morbidity and mortality in the comparison vaginal progesterone versus placebo. Second, data for 14 patients with a singleton gestation, previous preterm birth, and cervical length <25 mm who participated in a trial[120] that compared Shirodkar cerclage, McDonald cerclage, and bed rest (no cerclage) could not be obtained from the investigators. It was not possible to determine how many of these patients had a previous spontaneous preterm birth. In this trial,[120] a total of 104 women with no signs of infection or inflammation of the lower genital tract and a cervical length <25 mm between 16 and 26 weeks of gestation were randomly allocated to one of the three

groups. Overall, there were no significant differences between the cerclage and no cerclage groups in the risk of preterm birth and adverse perinatal outcomes. It is very unlikely that the significant beneficial effects of cerclage on the risk of preterm birth and perinatal morbidity and mortality become non-significant after the inclusion of data from this study in the meta-analyses. Third, 20% of women in the control group of trials evaluating cerclage received 17-OHPC compared with none in the control group of trials evaluating vaginal progesterone. This difference could potentially mean that the control groups, which were used as the common comparator, are not similar. Notwithstanding, the sensitivity analysis performed by excluding these patients showed no significant differences in the results obtained with overall meta-analyses. In addition, there is no evidence that 17-OHPC can decrease the risk of preterm birth in women with a singleton gestation and a short cervix.[124-126] Finally, maternal side effects associated with cerclage use such as vaginal discharge, infection, and bleeding were not reported in the IPD meta-analysis that evaluated this intervention,[82] which precluded comparisons with those reported in trials that evaluated vaginal progesterone.

Maternal adverse events and long-term childhood outcomes related to interventions

At the time of translating the results from this updated indirect comparison meta-analysis into practice, some considerations are necessary. Given the apparent similar efficacy between vaginal progesterone and cerclage, differences in maternal adverse events and long-term childhood outcomes are key variables that clinicians and patients with a singleton gestation and previous spontaneous preterm birth should consider when selecting an optimal treatment for a

sonographic short cervix in the midtrimester. Cerclage placement has been associated with complications such as rupture of membranes, chorioamnionitis, bleeding, and cervical lacerations.[86] Additionally, cerclage is a surgical intervention which is usually performed under general or spinal anesthesia, and as such is at risk of surgical complications. The trial by Owen et al,[116] which contributed 60% of patients to the IPD meta-analysis that evaluated cerclage,[82] reported that surgical and anesthetic complications that were associated with cerclage placement were uncommon. The Cochrane review that assessed the use of cerclage for preventing preterm birth in women with singleton gestations at high risk for this entity reported that cerclage, compared with no treatment, significantly increased the rates of maternal fever (6% versus 2%; RR, 2.39, 95% CI, 1.35-4.23) and cesarean delivery (18% versus 15%; RR, 1.19; 95% CI, 1.01-1.40).[123] Moreover, cerclage was associated with a non-significant increase in the risk of maternal side effects (vaginal discharge, bleeding, or pyrexia not requiring antibiotics; RR, 2.25; 95% CI, 0.89-5.69).

Several systematic reviews and meta-analyses that evaluated the efficacy and safety of vaginal progesterone for preventing preterm birth in singleton and twin gestations, have reported that the rates of maternal adverse events, discontinuation of treatment because of adverse effects, and congenital anomalies did not differ significantly between the vaginal progesterone and placebo/no treatment groups.[70,81,127-129] With regard to long-term childhood outcomes, current evidence suggests that in-utero exposure to vaginal progesterone, administered in singleton or twin gestations for the prevention of preterm birth, has no any harmful effect on neurodevelopmental outcomes at least until 8 years of age.[91,130-134] No

studies have reported on long-term neurodevelopmental outcomes in children whose mothers received a cerclage.[134]

Cost-effectiveness of interventions

Evidence from several studies indicates that the combination of universal transvaginal cervical length screening and vaginal progesterone administration to women with a short cervix is a cost-effective intervention that reduces preterm birth and perinatal morbidity and mortality.[135-144] Moreover, emerging evidence from recent studies conducted in hospitals located in the United States[144-146] and one Australian state[147] suggests that the implementation of universal cervical length screening and vaginal progesterone administration to patients with a sonographic short cervix is associated with a significant reduction in the rates of preterm birth. Several of these studies included women with a previous spontaneous preterm birth.[135,139,140,142,143,146-148]

We identified three studies, all published in abstract form only, which have evaluated the cost-effectiveness of cerclage in women with a short cervix.[149-151] In 2011, Miller and Grobman[149] compared 17-OHPC alone versus ultrasonographic cervical length screening with cerclage placement for women with a cervical length <15 mm. This strategy was more costly and less effective than the 17-OHPC only strategy. The authors concluded that "cervical length screening for possible cerclage placement is not, under most circumstances, a cost-effective strategy to prevent recurrent preterm birth". In 2015, Eke et al[150] evaluated the cost-effectiveness of vaginal progesterone compared to cerclage in patients with a sonographically short cervix. Treatment with vaginal progesterone, as compared to cerclage, was associated with lower incidence of preterm birth and resulted in

better efficacy. In 80% of simulations, vaginal progesterone was cost saving in comparison with cerclage. The authors of this study concluded that vaginal progesterone was the most cost effective strategy in treating women with a short cervix. Finally, Gray et al[151] performed a decision and cost analysis about serial cervical length screening in women with a singleton gestation and a previous spontaneous preterm birth. Patients with a cervical length ≤25 mm would be treated with vaginal progesterone, cerclage or a pessary. This study reported that cervical length screening and treatment with cerclage was the most costly strategy but was the most effective in reducing preterm births.

Clinical practice guidelines

Currently, the National Institute for Health and Care Excellence,[74] recommends offering either vaginal progesterone or cerclage to women with a singleton gestation, previous spontaneous preterm birth and a midtrimester cervical length <25 mm. The International Federation of Gynecology and Obstetrics recommends vaginal progesterone in women with a singleton gestation and a cervical length ≤25 mm regardless of obstetrical history.[73] The Society for Maternal-Fetal Medicine,[84,87,152] and the American Congress of Obstetricians and Gynecologists[85,86] recommend considering the placement of a cerclage in patients with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm before 24 weeks of gestation. This recommendation was based mainly on the findings of the IPD meta-analysis that assessed the use of cerclage in women with these characteristics.[82] In a recently published viewpoint article,[88] Dr Vincenzo Berghella, the lead author of the IPD meta-analysis that evaluated the efficacy of cerclage in women with a singleton gestation, previous spontaneous

preterm birth, and a cervical length <25 mm, wrote about his study that "*after 17 years of collaborative research, a meta-analysis of randomized controlled trials on cerclage for singleton gestations with a prior spontaneous preterm birth and with a short transvaginal ultrasound cervical length <25mm before 24 weeks led to new clinical recommendations worldwide. This is an example of the power of meta-analyses, of why I like them, and why I think you should like them too. Many societies rank meta-analyses of randomized controlled trials as the best level of evidence, even above that of a single randomized controlled trial*". We strongly agree with Dr Berghella's statement and believe that the same applies to both our updated IPD meta-analysis showing that vaginal progesterone also decreases preterm birth and improves perinatal outcomes in patients with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm, and our updated adjusted indirect comparison meta-analysis demonstrating that vaginal progesterone and cerclage are equally efficacious in preventing preterm birth in these patients. Therefore, professional/scientific organizations need to revise their recommendations to clinicians, based on the available evidence and recommend that vaginal progesterone be offered as an alternative to cerclage in patients with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm before 24 weeks of gestation.

Implications for practice

In summary, either vaginal progesterone or cerclage can be used for preventing preterm birth and improving perinatal outcomes in patients with a singleton gestation, previous spontaneous preterm birth, and a midtrimester sonographic short cervix. Thus, other criteria besides efficacy may play a role in therapeutic

decision-making, including maternal adverse events and cost-effectiveness of interventions, and the patient and physician's preferences.

Implications for research

Adequately powered randomized controlled trials directly comparing vaginal progesterone and cerclage would provide the best estimates of efficacy, but such trials would require a large sample size given the relatively similar efficacy of these interventions. These studies should determine the cost-effectiveness of interventions and assess the long-term effects of these strategies on childhood outcomes. In the interim, we believe that our indirect comparison meta-analysis represents the best available evidence for consideration in guiding clinical practice.

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TABLE 1. Characteristics of studies included in the indirect comparison meta-analysis

Study, year	Trial enrolment	Participants randomly assigned in original trial	Participants eligible for ICMA	Treatment groups	Primary outcome
Vaginal progesterone compared with placebo					
Fonseca,[108] 2007	8 centers in United Kingdom, Chile, Brazil, and Greece	250 with a singleton or twin gestation and a cervical length ≤15 mm	38	Vaginal progesterone 200 mg/day or placebo from 24-33 6/7 weeks of gestation	Spontaneous preterm birth <34 weeks
O'Brien,[109] 2007	53 centers in United States, South Africa, India, Czech Republic, Chile, and El Salvador	659 with a singleton gestation and previous spontaneous preterm birth	22	Vaginal progesterone 90 mg/day or placebo from 18-22 to 37 0/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first	Preterm birth ≤32 weeks
Cetingoz,[110] 2011	Single center in Turkey	160 with twin gestation, or singleton gestation with previous spontaneous preterm birth, or uterine malformation	6	Vaginal progesterone suppository 100 mg/day or placebo from 24-34 weeks of gestation	Preterm birth <37 weeks
Hassan,[111] 2011	44 centers in United States, Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, and Ukraine	465 with a singleton gestation and a cervical length between 10-20 mm	92	Vaginal progesterone 90 mg/day or placebo from 20-23 6/7 to 36 6/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first	Preterm birth <33 weeks
Norman,[91] 2016	66 centers in United Kingdom and Sweden	1228 with a singleton gestation and previous spontaneous preterm birth, or cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth	107	Vaginal progesterone 200 mg/day or placebo from 22-24 to 34 weeks of gestation or preterm delivery, whichever occurred first	Preterm birth <34 weeks or fetal deat composite of death bronchopulmonary dysplasia or brain injury; and cognitive composite score at years of age

Cerclage compared with no cerclage					
Rust,[112] 2001	Single center in United States	113 with a singleton or multiple gestation and transvaginal sonographic dilation of the internal os with either membrane prolapse into the endocervical canal at least 25% of the total cervical length but not beyond the external os or a cervical length <25 mm	102	McDonald procedure with a single stitch of permanent monofilament or no cerclage	Gestational age at delivery and neonat morbidity
Althuisius,[113] 2001	Single center in The Netherlands	36 with a singleton gestation, risk factors and/or symptoms of cervical incompetence, and a cervical length <25 mm	26	McDonald procedure with braided polyester thread or no cerclage	Preterm birth <34 weeks, and neonat morbidity and mortality
To,[114] 2004	12 centers in United Kingdom, Brazil, South Africa, Slovenia, Greece, and Chile	253 with a singleton gestation and a cervical length ≤15 mm	44	Shirodkar suture with mersilene tape or no cerclage	Preterm birth <33 weeks
Berghella,[115] 2004	2 centers in United States	61 with a singleton or twin gestation and a cervical length <25 mm or funneling >25%	31	McDonald procedure with mersilene tape or no cerclage	Preterm birth <35 weeks
Owen,[116] 2009	15 centers in United States	302 with a singleton gestation, previous spontaneous preterm birth, and cervical length <25 mm	301	McDonald procedure with nonabsorbable suture (braided tape) or no cerclage	Preterm birth <35 weeks

ICMA, indirect comparison meta-analysis

TABLE 2. Direct comparisons: vaginal progesterone versus placebo and cerclage versus no cerclage

	Vaginal progesterone versus placebo						Cerclage versus n			
Outcome	No. of trials	Vaginal progesterone	Placebo	RR (95% CI)	Heterogeneity I^2 (%)	NNT (95% CI)	No. of trials	Cerclage	No cerclage	RR (95
Primary outcomes										
Preterm birth <35 weeks	5	44/139 (32%)	58/126 (46%)	0.68 (0.50-0.93)	0	7 (4-31)	5	71/250 (28%)	105/254 (41%)	0.70 (0
Perinatal mortality	5	7/139 (5%)	10/126 (8%)	0.63 (0.26-1.56)	0	---	5	22/250 (9%)	35/254 (14%)	0.65 (0
Secondary outcomes										
Preterm birth <37 weeks	5	67/139 (48%)	74/126 (59%)	0.82 (0.65-1.02)	0	---	5	105/250 (42%)	154/254 (61%)	0.70 (0
Preterm birth <32 weeks	5	27/139 (19%)	40/126 (32%)	0.60 (0.39-0.92)	0	8 (5-39)	5	48/250 (19%)	75/254 (30%)	0.66 (0
Preterm birth <28 weeks	5	18/139 (13%)	23/126 (18%)	0.68 (0.39-1.19)	0	---	5	32/250 (13%)	51/254 (20%)	0.64 (0
Respiratory distress syndrome	4	3/75 (4%)	12/83 (14%)	0.38 (0.13-1.07)	7	---	4	13/207 (6%)	21/196 (11%)	0.61 (0
Grade III/IV intraventricular hemorrhage	5	1/137 (1%)	3/126 (2%)	0.50 (0.08-2.96)	8	---	4	0/207 (0%)	4/196 (2%)	0.28 (0
Necrotizing enterocolitis	5	3/137 (2%)	3/126 (2%)	0.84 (0.19-3.77)	0	---	4	1/207 (1%)	2/196 (1%)	0.62 (0
Neonatal sepsis	5	5/137 (4%)	13/126 (10%)	0.38 (0.15-0.96)	0	16 (11-242)	4	8/207 (4%)	17/196 (9%)	0.47 (0
Bronchopulmonary dysplasia	3	5/113 (4%)	6/90 (7%)	0.61 (0.20-1.83)	0	---	1	7/135 (5%)	6/127 (5%)	1.10 (0
Composite neonatal morbidity[c]	4	3/75 (4%)	16/83 (19%)	0.29 (0.11-0.81)	0	7 (6-27)	4	17/207 (8%)	28/196 (14%)	0.60 (0

Composite perinatal morbidity/mortality[d]	4	7/75 (9%)	20/83 (24%)	0.43 (0.20-0.94)	0	7 (5-69)	5	39/250 (16%)	63/254 (25%)	0.64 (0
Admission to NICU	5	26/138 (19%)	51/126 (40%)	0.46 (0.30-0.70)	0	5 (4-8)	4	57/207 (28%)	67/196 (34%)	0.63 (0
Birthweight <2500 g	5	56/139 (40%)	65/126 (52%)	0.78 (0.59-1.02)	0	---	5	86/250 (34%)	117/249 (47%)	0.65 (0
Birthweight <1500 g	5	24/139 (17%)	31/126 (25%)	0.67 (0.42-1.08)	0	---	5	42/250 (17%)	66/249 (27%)	0.64 (0

CI, confidence interval; *NICU*, neonatal intensive care unit; *NNT*, number needed to treat; *RR*, relative risk

[a] For the Mantel-Haenszel Q statistics (test of heterogeneity); [b] For the test of association; [c] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia; [d] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal death

TABLE 3. Indirect comparison: vaginal progesterone versus cerclage

	Vaginal progesterone versus cerclage	
Outcome	**RR (95% CI)[a]**	***P* value[b]**
Primary outcomes		
Preterm birth <35 weeks	0.97 (0.66-1.44)	0.93
Perinatal mortality	0.97 (0.35-2.69)	0.96
Secondary outcomes		
Preterm birth <37 weeks	1.17 (0.88-1.56)	0.61
Preterm birth <32 weeks	0.91 (0.53-1.55)	0.79
Preterm birth <28 weeks	1.06 (0.53-2.11)	0.89
Respiratory distress syndrome	0.62 (0.18-2.16)	0.84
Grade III/IV intraventricular hemorrhage	1.79 (0.15-22.00)	0.76
Necrotizing enterocolitis	1.36 (0.11-16.89)	0.84
Neonatal sepsis	0.81 (0.24-2.76)	0.76
Bronchopulmonary dysplasia	0.56 (0.12-2.57)	0.49
Composite neonatal morbidity[c]	0.48 (0.15-1.53)	0.75
Composite perinatal morbidity/mortality[d]	0.67 (0.29-1.57)	0.86
Admission to NICU	0.73 (0.34-1.55)	0.38
Birthweight <2500 g	1.20 (0.72-2.00)	0.56
Birthweight <1500 g	1.05 (0.58-1.88)	0.90

CI, confidence interval; *NICU*, neonatal intensive care unit; *RR*, relative risk

[a] RR <1 favors vaginal progesterone and RR >1 favors cerclage; [b] For the test of association; [c] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia; [d] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal death

TABLE 4. Subgroup and sensitivity analyses

	Direct comparisons						Indirect comparison	
	Vaginal progesterone versus placebo			Cerclage versus no cerclage			Vaginal progesterone versus cerclage	
Outcome	**Vaginal progesterone**	**Placebo**	**RR (95% CI)**	**Cerclage**	**No cerclage**	**RR (95% CI)**	**RR (95% CI)**	***P* value**[a]
Women with a cervical length <16 mm								
Preterm birth <35 weeks	22/58 (38%)	31/55 (56%)	0.64 (0.42-0.98)	28/80 (35%)	43/74 (58%)	0.59 (0.42-0.83)	1.09 (0.63-1.87)	0.87
Preterm birth <32 weeks	18/58 (31%)	23/55 (42%)	0.69 (0.42-1.14)	18/80 (23%)	33/74 (45%)	0.50 (0.32-0.78)	1.38 (0.71-2.69)	0.54
Perinatal mortality	2/58 (3%)	5/55 (9%)	0.39 (0.10-1.51)	11/80 (14%)	16/74 (22%)	0.59 (0.31-1.14)	0.66 (0.15-2.98)	0.67
Women without co-interventions for a short cervix								
Preterm birth <35 weeks	35/117 (30%)	53/118 (45%)	0.66 (0.47-0.94)	57/203 (28%)	85/201 (42%)	0.67 (0.51-0.88)	0.99 (0.63-1.53)	0.97
Preterm birth <32 weeks	21/117 (18%)	37/118 (31%)	0.57 (0.36-0.91)	40/203 (20%)	64/201 (32%)	0.63 (0.45-0.88)	0.91 (0.51-1.60)	0.80
Perinatal mortality	6/117 (5%)	10/118 (8%)	0.58 (0.22-1.51)	19/203 (9%)	33/201 (16%)	0.58 (0.35-0.98)	1.00 (0.34-2.98)	1.00

CI, confidence interval; *RR*, relative risk

[a] For the test of association