



Twin Pregnancy Gestational Length Prolongation and Neonatal Morbidity and Mortality Reduction by Cervical Pessary with or without Vaginal Progesterone

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Abstract

Purpose: The purpose of this mini review is to elucidate if cervical pessary, with or without progesterone is applicable to twin pregnancies. One-quarter of preterm births (PTB) are twin pregnancies. Cervical cerclage, progesterone, and cervical pessary decrease the PTB incidence in singleton pregnancies. Retrospective cohorts suggest that cervical cerclage is not harmful, and is possibly beneficial in twin pregnancies, whereas meta-analysis found cervical cerclage harmful in twin pregnancies.

Methods: Three significant articles from January to April, 2016 were selected for evidence-based practice review. Hand search was performed as needed to complete the subject background.

Results: An American retrospective case-control study suggests that the Arabin cervical pessary with vaginal progesterone reduces twin pregnancy PTB at < 34 weeks estimated gestational age (EGA), to 23.8% from 44.4% for controls. The mean cervical length was ≤ 11 mm at 25 weeks mean EGA. A European multicenter randomized control trial (RCT) reduced PTB at < 34 weeks EGA, from 40.9% in controls to 17.6% in Arabin pessary patients, $p = .002$. However, an international RCT found equivalent PTB rates at < 34 weeks EGA, 13.6% in Arabin pessary patients and 12.9% in controls, accompanied by similar neonatal morbidity and mortality, and similar proportions of newborn birth weight < 2,500 grams.

Conclusion: The Arabin cervical pessary with, or without vaginal progesterone may be most beneficial in twin pregnancies with cervical length ≤ 11 mm. Further RCT are needed to clarify which PTB prevention modalities are most beneficial in twin pregnancy. Twin Pregnancy Gestational Length Prolongation and Neonatal Morbidity and Mortality Reduction by Cervical Pessary with or Without Vaginal Progesterone Twin pregnancies lead to 25% of preterm births (PTB), but are 1.5% of all pregnancies [1]. The twin pregnancy gestational age-based PTB rate can be 5 to 10 times that of singleton pregnancies [2]. The increased risk of PTB in twin pregnancies, in turn, proportionally raises perinatal morbidity and mortality compared to that of singleton pregnancies [3]. Twin pregnancies' rising incidence from 19.8 to 33.1 per 1,000 births from 1980 to 2012 compounds the incidence of perinatal morbidity and mortality attributed to twin, not singleton pregnancies [4]. Three mechanisms exist to reduce PTB in singleton pregnancies: Cervical cerclage, progesterone, and cervical pessary (Table 1). Of these, it is possible that only cervical pessary with or without progesterone prevents PTB in twin pregnancies.

Keywords: Twin pregnancy; Neonatal morbidity; Cervical pessary; Vaginal progesterone

Mechanisms to Prevent Preterm Birth

Cervical cerclage

Cervical cerclage mechanically closes the cervix. Cervical cerclage is the gold standard prophylaxis for recurrent PTB in singleton pregnancies [3,5]. Cervical cerclage halves the singleton PTB rate in women with three or more PTB or second-trimester spontaneous abortions from 32% to 15%, $p = .02$ [6]. Cervical cerclage placed in singleton pregnancies with cervical length (CL) < 25 mm at 16 to 22 6/7 weeks estimated gestational age (EGA) reduces birth at less than 37 weeks ($p = .01$), birth at less than 24 weeks ($p = .03$), and perinatal mortality ($p = .01$), when there is a history of one or more PTB [6]. While retrospective cohorts suggest cervical cerclage may clinically and statistically significantly reduce twin pregnancy PTB rate and neonatal morbidity and mortality, no benefit is seen from rescue cerclage [7-9]. The PTB increased two fold in randomized

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controlled trial (RCT) subgroup meta-analysis of twin pregnancy cervical cerclage. Therefore, twin pregnancy cervical cerclage is discouraged [7].

Progesterone

Progesterone's myometrial relaxation is associated with cervical ripening prevention, in turn preventing cervical dilation and fetal delivery [2]. Weekly 17-hydroxyprogesterone, 250 µg injection, reduces singleton pregnancy PTB in women with a previous PTB by one-third [5,6,10]. When treating singleton active preterm labor, twice weekly 17-hydroxyprogesterone, 341 µg injections reduce PTB, odds ratio (OR) = .15; 95% confidence interval (CI) = .04 to .58 [2]. Vaginal progesterone, 90 mg/d of an 8% gel, equivalent to 200 mg daily, reduces early preterm birth ($p = .014$), neonatal intensive care admissions (NICU; $p = .016$), and length of NICU stay ($p = .013$), in women with previous PTB and singleton pregnancy with a CL < 15 mm [2].

Cervical pessary

In the United States, the introduction of patented 17-hydroxyprogesterone priced at USD 1,440 per weekly dose, and attempted removal of compounded 17-hydroxyprogesterone costing USD 15 per weekly dose from the marketplace, resulted the use of infertility formulation vaginal progesterone and urogenital prolapse pessaries or pessaries designed to treat cervical incompetence as alternative PTB prophylaxis [5,11,12]. Cervical pessary efficacy shows biologically plausible analogy [13]. The cervical pessary is designed to keep the cervix elongated and closed, similar to cervical cerclages' purse string like cervical closure. Initially shown by the Bakelite ring in 1959, like cerclages, cervical pessaries mechanically close the cervix, elevating the fetal head off the cervix [14]. The Hodge and Smith lever pessaries were also used successfully to prevent singleton PTB [14,15]. Subsequently, the bulkier Hamann/Jorde and Mayer-Ring pessaries were used. Thereafter, the incontinence dish pessary like Arabin-cerclage pessary has been used to prevent singleton PTB [14,16,17]. Simultaneously, Hodge pessaries were used with tocolytics to prevent multiple gestations PTB [14].

In singleton pregnancies with CL ≤ 25 mm, cervical cerclage, cervical pessary, and vaginal progesterone have equal efficacy [18]. The Pro TWIN trial suggests that cervical pessary can prevent PTB in twin pregnancies with short CL [19]. However, cervical cerclage is not currently recommended for multiple gestation PTB prevention, and is the most invasive of the three PTB prevention options [7]. Therefore, this mini review seeks to determine if cervical pessary or cervical pessary with vaginal progesterone, compared to no intervention, can reduce neonatal morbidity and mortality and twin pregnancy PTB at less than 34 weeks EGA.

Methods

In 2016, two multicenter RCTs, each notated as a report of major impact, were published [1,4]. Also in 2016, a retrospective case-control study on twin pregnancy PTB prevention was found worthy of editorial [19,20]. These three studies were selected for evidence-based practice (EBP) mini review. Hand search was performed as needed to provide the milieu for these works and the EBP consideration.

Results

Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (pecep-twins)

Five Spanish hospitals were trial sites for this registered,

prospective, un-blinded RCT [4]. Blinding a pessary trial is impossible as inert, placebo pessaries are non-existent. Patients with anatomically and physiologically normal twin pregnancies and CL ≤ 25 mm at the second trimester ultrasound (18 to 22 weeks EGA) were eligible. Patients with prior cervical conization or who had already received a cervical cerclage in the current pregnancy, and patients with complicated pregnancies such as vaginal bleeding or abnormal placentation were excluded [4]. Cervical length measurement was standardized and centrally reviewed. From January 2011 through July 2014, 2,287 twin pregnancies were scanned, of which 154 had CL ≤ 25 mm. The included 137 pregnancies were randomized by computer generated variable blocks of 2 to 4 to pessary or no treatment control in a 1:1 ratio, resulting in 68 pessary and 66 expectant management patients. Three patients lost to follow-up were not included in analyses [4]. A standard 65 x 25 x 32 mm Arabin pessary was used, except for patients intolerant of this pessary, who then received a pessary fitting [4,21]. Both groups were demographically and obstetrically similar at study start. The groups received otherwise identical obstetric care [4].

The primary outcome, PTB at less than 34 weeks EGA, occurred in 12 (17.6%) pessary and 27 (40.9%) control patients, $p = .002$, relative risk (RR) .43, 95% CI .24 to .78 [4]. This is a 2.3 fold reduction in PTB. Birth weight < 2,500 grams occurred more often in the control group (62 cases) than the pessary group (47 cases), $p = .01$, RR .72, 95% CI .54 to .97. Composite neonatal morbidity was not statistically different between groups, despite two fetal deaths in the control group, whereas the pessary group had neither fetal nor neonatal deaths. All patients in the pessary group had vaginal discharge, a known adverse effect of pessary use [4,22].

A potentially comparable singleton pregnancy cerclage pessary trial was limited by possible selection bias as about half of eligible patients choose not to enroll in the trial [23]. Arguably underpowered, and stopped early due to slow accrual, this singleton pregnancy trial achieved a 20.7% singleton pregnancy PTB rate at less than 34 weeks EGA, which is comparable to that achieved by the PECEP-Twins trial [4,11,23]. Although multiple pregnancies normally deliver earlier than singleton pregnancies, this suggests that while the design and methods of the PECEP-Twins trial appear appropriate, bias, chance, or confounding may be present [4]. However, based on the PECEP-Twins trial, a pessary should be offered to patients with twin pregnancy and CL ≤ 25 mm on the second trimester ultrasound. A 44% reduction in twin pregnancy PTB before 34 weeks EGA, and a 25% reduction in birth weights < than 2,500 grams are worth enduring vaginal discharge for at most 18-22 weeks and the up to USD 125 cost of a pessary [24].

Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: A randomized controlled trial

Cervical pessary placement in twin pregnancies of unknown cervical length was the intervention and no treatment was the control in this 23 hospital, international, registered RCT [1]. Patients with anatomically normal twin pregnancies on second trimester ultrasound from August 2008 through May 2011 were eligible. Exclusion criteria were consistent with the PECEP-Twins trial [4]. From 2,107 eligible patients, 1,180 were randomized to groups, 3 were lost to follow-up. Patients were randomized 1:1 to Arabin cervical pessary or no treatment, via a random-number list instead of blocks, resulting in 590 patients in each group. Both groups were demographically and obstetrically similar at study start. The groups received identical obstetric care [1].

Intention to treat analysis was performed, which is important as 31 pessaries were removed early on patient demand. The primary outcome, PTB at less than 34 weeks EGA, occurred in 80 (13.6%) pessary and 76 (12.9%) control patients, RR 1.054, 95% CI .899 to 1.051. Birth weight < 2,500 grams occurred similarly in each group, RR .972, 95% CI .54 to .97 [1]. Neonatal morbidity and mortality was similar in the study groups. Post hoc analysis of 214 patients with CL \leq 25 mm did not show any significant differences with PTB at < 34 weeks occurring in 33 of 106 (31.1%) pessary patients and 28 of 108 (25.9%) expectant management patients. Selection bias may have occurred as almost half of the eligible patients choose not to participate [1].

Lack of standardized training in cervical pessary insertion may be a study weakness. Blinded, centralized computer randomization, standardized ultrasounds, and adherence to protocol are study strengths. The post hoc analysis for patients with CL \leq 25 mm is inconsistent with findings in the literature [1]. Based on this study, cervical pessary would not be recommended for all patients with twin pregnancies.

Cervical pessary and vaginal progesterone in twin pregnancies with a short cervix

An electronic health record search to review anatomically normal twin pregnancies at 28 weeks EGA or less with CL \leq 20 mm that did not receive a cervical cerclage formed the basis of this retrospective case control study [19]. Three controls were selected based on EGA and CL for each intervention case. Lack of controls with anatomically normal fetuses and without cervical cerclage led to exclusion of an intervention patient [19]. The study comprised 21 cases with Arabin cervical pessaries and vaginal progesterone from 2013 to 2015, and 63 controls who received vaginal progesterone from 2005 to 2013. Cases and controls received identical obstetric care [19].

Consistent with the preceding studies, blinding could not occur [1,4,19]. Other than increased monochorionicity and in-vitro fertilization pregnancies in the intervention group, the groups were demographically and obstetrically similar. Regression analysis and adjusted p values adjusted for these confounders. Due to the mean CL of 10-11 mm, except for subgroup analysis, this study population is different from the preceding studies [1,4,19]. PTB at < 34 weeks EGA was clinically but not statistically significantly different between groups, 23.8% for cases and 44.4% for controls, adjusted p = .1 [19]. Smaller twins' weights were significantly less, adjusted p = .024, and composite morbidity and mortality were significantly worse, adjusted p = .04 in the control group [19]. Control outcomes could have been adversely affected by obstetric and neonatal standard of care changes from 2005 to 2015, and the control longer follow-up time, permitting greater incidence of adverse outcomes. Improvements in obstetric and neonatal care, including improved use of antenatal steroids for fetal lung maturity, assisted ventilation, neonatal intensive care, surfactant, and prenatal multivitamin formulation may have affected the outcomes from 2005 to 2015 [25]. Improved obstetric and prenatal care may be reflected in improved periviable and extremely low birth weight newborn survival in Australia from 1979 - 1997 and the United Kingdom from 1995 - 2006 [25].

A cohort study would be an appropriate method to answer the question, whether cervical pessary with vaginal progesterone is more effective than vaginal progesterone alone to prevent PTB in twin pregnancy, if the cases and controls received interventions simultaneously not sequentially. Vaginal progesterone and cervical

pessary can be offered in clinical practice, as an association between improved neonatal outcomes and cervical pessary use has been shown [19]. However, confounding by improved obstetric and neonatal care, and reduced adverse outcome reporting and documentation within shorter follow-up periods for intervention participants cannot be excluded.

Conclusion

The quality of the available evidence and outcomes are variable (Table 1). The results from these studies do not fit with each other [1,4,19]. Direct comparison can be made between PECEP-Twins trial and the International RCT post hoc analysis, but, the retrospective case-control study is not directly comparable to either preceding study [1,4,19]. The retrospective case control study used a later baseline EGA (28 weeks instead of 18-22 weeks) for intervention initiation, and a shorter CL (\leq 20 mm instead of \leq 25 mm) [19]. Despite these negative handicapping differences, the retrospective case control study pessary with vaginal progesterone arm achieved comparable reductions in PTB at \leq 34 weeks EGA to the PECEP-Twins trial [4,19]. The Arabin cervical pessary with, or without vaginal progesterone may be most beneficial in twin pregnancies with CL \leq 11 mm, but still useful in twin pregnancies with CL \leq 25 mm on second trimester anatomy ultrasound from 18 - 28 weeks EGA. Future studies could evaluate cervical pessary efficacy with and without vaginal progesterone, initiated later than 22 weeks EGA at a range of CLs \leq 25 mm for prevention of PTB before 34 weeks EGA in twin pregnancy. Such studies may reveal a time sequence response and a CL association [13]. International RCT of cervical pessary in twin pregnancies with CL \leq 25 mm at 18-22 weeks EGA are needed to validate or refute the PECEP-Twins trial and the International RCT post hoc analysis [1,4].

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