

ORIGINAL ARTICLE

Tocolytics used as adjunctive therapy at the time of cerclage placement: a systematic review

J Smith^{1,2} and EA DeFranco^{3,4}

OBJECTIVE: To review the published literature on whether the use of empiric perioperative tocolytic medications could provide additional benefit when used in combination with cerclage.

STUDY DESIGN: Systematic review of published medical literature reporting the efficacy of empiric tocolytics used as a perioperative adjunct to vaginal cerclage in high-risk patients. A PubMed search without date criteria of various tocolytics and cerclage yielded 42 studies. Review articles were excluded, as were reports of abdominal cerclage, emergent cerclage, or cerclage for the purpose of delayed interval delivery in twin gestations.

RESULT: Only five publications on the topic of perioperative tocolytic use at the time of history or ultrasound-indicated vaginal cerclage placement were identified. These included zero clinical trials, three retrospective cohort studies, one case series and one case report. Only one cohort study compared cerclage with indomethacin and cerclage without indomethacin and suggested no difference between the groups. The other two published cohort studies had no referent group who received cerclage without tocolysis. One case series and one case report were also published reporting cerclage with empiric beta-mimetic and progesterone adjunctive therapy.

CONCLUSION: There is a paucity of published data on the topic of adjunctive perioperative tocolytics with cerclage. Adequately powered clinical trials on perioperative use of tocolysis with cerclage compared with a standard cerclage placement alone are needed to establish efficacy. Until adequately studied, this practice should be considered investigational.

Journal of Perinatology (2015) **35**, 561–565; doi:10.1038/jp.2015.38; published online 23 April 2015

INTRODUCTION

Preterm birth is one of the most vexing complications of pregnancy, affecting ~11% of all births.¹ Cervical cerclage has been shown to decrease the rate of preterm birth in some subgroups of high-risk patients.^{2–4} However, despite the overall efficacy of cerclage, a substantial number of women deliver before term despite cerclage placement. Whether the addition of other perioperative interventions such as tocolytic medications could provide additional benefit when used in combination with cerclage to minimize uterine activity remains unanswered.^{5,6} We aim to systematically review the available published medical literature to identify evidence supporting the addition of prophylactic tocolytic medications used as an adjunctive therapy to improve the efficacy of cervical cerclage for preterm birth prevention.

METHODS

For this systematic review, our aim was to identify whether there is evidence to support the efficacy of perioperative tocolytic agents used at the time of history or ultrasound-indicated prophylactic vaginal cerclage used as a preventive measure for preterm birth. We focused on the use of adjunctive tocolytic medications given in addition to cerclage proximate to the time of its placement in routine or asymptomatic cases. Therefore, we did not include studies in which tocolytic agents were added after patients with cerclage later developed preterm contractions or other pregnancy

complications. Likewise, we did not include studies of exam-indicated or 'emergency' cerclage placement, as this population likely represents a group more likely to have underlying preterm labor physiology before cerclage placement.

In order to define 'adjunctive tocolytic therapy' for the purposes of this systematic review, we reviewed published clinical trials on the topic of prophylactic vaginal cerclage placement. We reviewed the methods of the 11 English language clinical trials included in the 2012 Cochrane review on cerclage in order to determine a standard for tocolytic therapy at the time of cerclage placement.² After review of the methods in which these cerclage procedures were performed in clinical trials, we determined that no tocolytic treatment at the time of cerclage would be considered the most common, and therefore the standard approach.

We performed a PubMed search without date criteria in August 2014 using the keywords 'atosiban and cerclage', 'beta mimetics and cerclage', 'terbutaline and cerclage', 'indomethacin and cerclage', 'magnesium and cerclage', 'nifedipine and cerclage' and 'calcium channel blocker and cerclage' with restriction to English language and human studies. These search criteria yielded 46 studies. Thirteen review articles were excluded, as were 11 articles on unrelated topics. Of the remaining 24 studies, four were excluded because they did not report the use of tocolytic medications as an adjunct in patients with cerclage,^{7–10} two were excluded as they were limited to transabdominal cerclage only,^{11,12} three were excluded because they involved delayed interval delivery of a second twin,^{13–15} and 10 were excluded because they reported exam indicated or 'emergent' cerclage rather than history or ultrasound-indicated cerclage placement.^{16–25} A bibliographic review of selected articles was also performed to search for additional studies that may have been missed with the original search

¹Wayne State University School of Medicine, Detroit, MI, USA; ²Children's Hospital of Michigan, Division of Genetic and Metabolic Disorders, Detroit, MI, USA; ³Division of Maternal-Fetal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA and ⁴Center for Prevention of Preterm Birth, Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. Correspondence: Dr EA DeFranco, Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 3255 Eden Avenue, 4820 Health Professions Building, Room 154, Cincinnati, OH 45267-0526, USA.

E-mail: emily.defranco@uc.edu

Presentation information: this study was presented as an poster presentation at the 81st Annual Meeting of the Central Association of Obstetricians and Gynecologists, 8 to 11 October 2014, Albuquerque, NM, USA.

Received 29 December 2014; revised 8 March 2015; accepted 18 March 2015; published online 23 April 2015

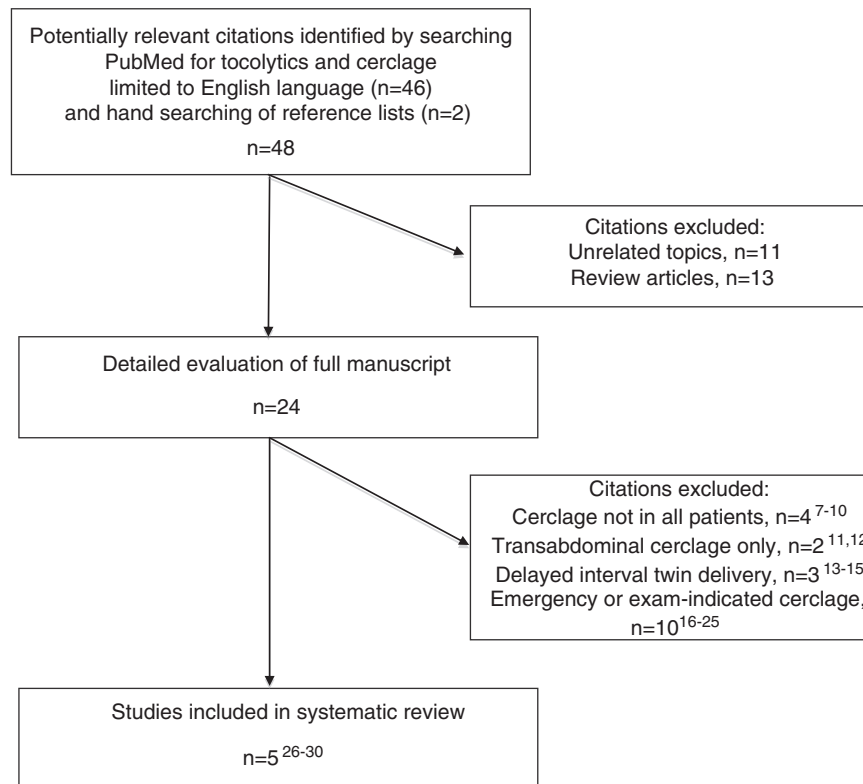


Figure 1. Systematic review flow diagram.

terms. Two additional articles were identified through a bibliographic review of publications on similar topics.^{26,27} This yielded a total of 5 studies for final review (Figure 1).²⁶⁻³⁰

RESULTS

Through this systematic review, we identified three retrospective cohort studies,²⁸⁻³⁰ one case series²⁶ and one case report²⁷ on the topic of perioperative tocolytic agents given at the time of cerclage placement (Table 1). There are no published clinical trials comparing the efficacy of prophylactic tocolytics given at the time of history-indicated or ultrasound-indicated cerclage compared with cerclage alone without perioperative tocolytics.

We identified four clinical studies that addressed the topic of indomethacin and cerclage. However, only two of these studies were in 'prophylactic' (history or ultrasound-indicated) cerclage patients, and therefore were included in this review.^{28,30} The other two studies, one retrospective cohort study¹⁷ and one randomized trial²⁰, were not included here because they studied indomethacin with 'emergent' or exam-indicated cerclage, which was an exclusion for this systematic review.

Only one retrospective cohort study has reported outcomes associated with indomethacin plus prophylactic cerclage placement compared with a reference group of women who received cerclage without prophylactic indomethacin administration. Visintine *et al.*³⁰ reported the influence of indomethacin in a group of patients who received an ultrasound-indicated cerclage on the basis of cervical length <25 mm between 14 and 23 weeks and 6 days. In this study, after exclusions and loss to follow-up, a total of 101 women who received an ultrasound-indicated cerclage were included in the analysis; 51 women received indomethacin at the time of ultrasound-indicated cerclage and 50 did not. The rate of spontaneous preterm birth before 35 weeks was similar

between those who received cerclage with indomethacin (20/51 (39%)) and those who received cerclage without indomethacin (17/50 (34%)). A *post hoc* power analysis revealed that the study was underpowered to assess the benefit of indomethacin in addition to cerclage, if a benefit did exist. However, the nearly null point estimate of effect found in this study, a relative risk of 1.15 (95% CI 0.69 to 1.93), suggests that even a larger sample size with a more precise confidence interval would not result in a conclusion that indomethacin in addition to cerclage would be associated with a significant reduction in preterm birth risk.

One additional cohort study examined the influence of indomethacin given at the time of ultrasound-indicated cerclage, but it was not compared with a reference group that received cerclage without indomethacin. In 2011, Kofinas and Kofinas²⁸ reported the outcomes of patients in their practice who were grouped into those with mild (26 to 34 mm), moderate (15 to 25 mm) and severe (<15 mm) degrees of shortened cervical length. Those with mild and moderate cervical shortening received bed rest alone or bed rest plus indomethacin, respectively. All patients who presented with 'severe' cervical shortening, <15 mm cervical length, received an ultrasound-indicated McDonald cerclage with bed rest and indomethacin for 1 week. After a week, if the cervix remained stable or improved, patients were switched to maintenance nifedipine therapy. During follow-up if the cervical length dropped below 25 mm, indomethacin was repeated. After the cerclage and the initial indomethacin treatment, 20 patients' cervixes lengthened and only one became shorter. Patients who were in the mild and moderate group, but then subsequently developed shorter cervical length <15 mm, also received cerclage in addition to indomethacin. All women who received cerclage and indomethacin ($n = 113$, 33%) had a mean latency to delivery of 18.3 weeks. However, there was no group that received only cerclage without

Table 1. Studies on the topic of empiric tocolysis given as a perioperative strategy with vaginal cerclage placement

Study	Design	Sample size	Cervical length cutoff for cerclage (mm)	Cerclage type	Mean gestational age (weeks)	Tocolytic	Mean latency to delivery (weeks)	Mean gestational age (weeks) at delivery	Outcome	Overall rate of PTB
Kofinas and Kofinas, 2011 ²⁸	Retrospective cohort ^a	21	<15	McDonald	20	Indomethacin	18.3			
Visintine, et al. 2008 ³⁰	Retrospective cohort	101	<25	Not specified	19 vs 19	Indomethacin, duration 48 h			PTB <35 wks	39% (indo) vs 35% (not)
Locci, et al. 2006 ²⁹	Retrospective cohort ^b	32	<30	McDonald	20–24	Atosiban vs ritodrine		33–39 vs 30–37		
Leo, et al. 1997 ²⁶	Case series	6		McDonald and Shirodkar		B-mimetic			Vital and viable fetus	75%
Watanabe, et al. 2012 ²⁷	Case report	1		Not specified	13	Ritodrine	27	40		

Abbreviations: PTB, preterm birth; wks, weeks gestational age. ^aNo reference group of cerclage without indomethacin for comparison. ^bNo reference group of cerclage without tocolytics. All patients with cerclage received either atosiban or ritodrine.

indomethacin for comparison to assess whether the latency was comparatively prolonged with the addition of indomethacin. Latency to delivery in those with cerclage and indomethacin appeared longer than in those with longer cervical lengths (mild and moderate groups); however, it is difficult to draw conclusions given the lack of a statistical comparison test result and the lack of a comparison group that received cerclage but no indomethacin. In addition, only 16% of women in the study had a prior preterm birth, which is the group most likely to benefit from cerclage.³¹ Therefore, those who received cerclage may have had a long latency even without cerclage or indomethacin, and latency duration cannot definitively be linked to either treatment *per se*.

A third retrospective cohort study on the topic of perioperative tocolytic administration with cerclage was published in 2006 by Locci *et al.* This study compared the perioperative use of atosiban ($n=16$) versus ritodrine ($n=16$) with ultrasound-indicated cerclage in pregnancies of singleton, twins and triplets conceived by ICSI.²⁹ Atosiban and ritodrine were used perioperatively (began preoperatively and extended through the postoperative period) for a total of 45–48 h. No patients in this study received cerclage without perioperative tocolytics for comparison. Empiric perioperative treatment with atosiban versus ritodrine was not associated with a difference in the primary outcomes, rate of delivery within 48 h or 7 days following cerclage placement. However, women receiving perioperative atosiban had a greater mean gestational age at delivery of 36 weeks compared with those who received perioperative ritodrine, who had a mean gestational age of 33 weeks ($P=0.001$). The earlier mean gestational age at delivery may have been influenced by the fact that three women delivered within 48 h of cerclage in the ritodrine group and only one delivered within 48 h in the atosiban group. However, given the small sample size, potential for selection bias, and no comparison group of cerclage without perioperative tocolytics, it is difficult to draw conclusions regarding the potential efficacy of either tocolytic as a perioperative treatment at the time of ultrasound-indicated cerclage placement.

There has been one case series published on the topic of empiric tocolytic use with vaginal cerclage placement. In 1997 Leo *et al.*²⁶ reported a case series of 86 patients who received a prophylactic cerclage due to the presence of a uterine anomaly (1978 to 1995). Forty patients with Shirodkar cerclage and 46 with McDonald cerclage were given beta mimetic and progesterone treatment from the sixteenth week onward. No patients in the case series received a cerclage without maintenance tocolytic therapy. Of patients included in this case series 75.6% delivered a viable fetus, 19.7% delivered between 14 and 26 weeks, and 4.6% aborted before 14 weeks. The authors reported their outcome as an improvement in viable pregnancies compared with previously reported data in patients with anomalous uterus without cerclage. However, no conclusion on the benefit of prophylactic beta mimetics in addition to cerclage can be drawn as there was no group that received cerclage without beta mimetic tocolytics to directly compare outcomes. In addition, the temporal relationship between gestational age at cerclage placement and when beta mimetics were started was not clearly presented in this report; therefore, whether they were given ‘perioperatively’ or weeks later ‘postoperatively’ as a maintenance therapy is unclear.

Finally, only one case report was identified through our review that reported empiric tocolytic use with prophylactic vaginal cerclage placement. In 2012, Watanabe *et al.*²⁷ presented a case report of a patient in Japan with C9 deficiency who previously had three mid-trimester spontaneous pregnancy losses and one early spontaneous miscarriage. The patient underwent a history-indicated cerclage at 13 weeks and received oral clindamycin for 1 week and intramuscular hydroxyprogesterone weekly throughout her pregnancy. She was also administered tocolysis with a continuous ritodrine infusion starting at 16 weeks, which

continued until 37 weeks. The patient delivered a viable infant at 40 weeks and 1 day. Although the outcome of the pregnancy in this report was improved compared with her prior pregnancies, it is unclear whether the cerclage, antibiotics, progesterone, or tocolytic contributed to the outcome, given the observational nature of this report. In addition, similar to the previously described case series, the later gestational age of 16 weeks at the time of tocolytic initiation, 3 weeks after cerclage was placed, brings into question whether this could be considered 'perioperative tocolytic use' or a 'maintenance tocolysis.'

DISCUSSION

A growing body of evidence supporting the benefit of cerclage in some subgroups of high-risk women^{2–4} in addition to published recommendations from the American College of Obstetricians and Gynecologists to identify cerclage candidates^{32,33} may lead to an increase in the frequency of pregnant women receiving cerclage in the US and elsewhere. Despite the already widespread use of cerclage for the prevention of preterm birth, the use of adjunctive perioperative tocolytics with cerclage has not been adequately studied. Whether the use of empiric perioperative tocolytics in combination with cervical cerclage can provide additional benefit remains unanswered.

Current published evidence to support various perioperative approaches to cerclage is limited by wide study heterogeneity, differences in study populations, cerclage indications, techniques and types of empiric treatments given.^{5,6} Through our systematic review of the current published literature on the topic of perioperative tocolytic use with history or ultrasound-indicated vaginal cerclage placement, we identified only one observational study that compared a group of patients who received a perioperative tocolytic (indomethacin) with cerclage and a reference group of women who received cerclage and no tocolytic.³⁰ The results of this study indicate that there is likely no benefit of indomethacin in these cases. Only two additional retrospective cohort studies have been published on the topic of tocolytics with cerclage in this patient population, but their results are less relevant to this question because neither compared outcomes with those in women who received cerclage without tocolytics.^{28,29} No clinical trials have been performed to assess the influence of perioperative tocolytics at the time of cerclage in these otherwise asymptomatic patients.

A randomized controlled trial was published by Miller *et al.*²⁰ in June 2014 investigating the use of indomethacin and prophylactic antibiotics in exam-indicated cerclage. Pregnant women with cervical dilation without regular uterine contractions were offered exam-indicated cerclage. If they accepted, they were offered enrollment in the study. Twenty-six women were randomized to receive indomethacin and prophylactic antibiotics (25 received cephazolin and one received clindamycin due to allergy). There were 24 women in the nonintervention group. The primary outcome of gestational latency after cerclage placement was not different between the two groups. However, there was a significant increase in the frequency of latency >28 days in the intervention group. This new evidence of efficacy may lead to an 'indication creep', where providers extrapolate the potential benefit of indomethacin observed in this study of women who presented with cervical dilation to a larger, but lower-risk population of history-indicated and ultrasound-indicated cerclage candidates. This is not without potential risk, given the concern regarding the risk of non-steroidal anti-inflammatory agents in some published studies.^{34–36} Furthermore, the lower likelihood of early delivery in asymptomatic women receiving cerclage for history or ultrasound-identified cervical shortening compared with women who undergo cerclage based on physical exam findings suggests that the potential benefit of additional perioperative tocolytics to these women would be smaller, if present at all.

The paucity of published data on this topic has led to wide variation in practice patterns when cerclage is indicated. Adequately powered clinical trials of perioperative use of tocolysis with cerclage compared with a standard cerclage placement alone are needed to answer the clinical question of whether they improve cerclage efficacy. Given the frequency with which cerclage is used in high-risk pregnancies, achieving this goal is certainly reasonable. Until adequately studied, the use of tocolytic agents as an adjunctive treatment at the time of history- or ultrasound-indicated cerclage placement should be considered investigational.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

ACKNOWLEDGMENTS

Financial support: Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; March of Dimes Grant 22-FY14-470.

REFERENCES

- Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. *Natl Vital Stat Syst* 2013; **62**: 1–20.
- Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev* 2012; **4**: CD008991.
- Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet Gynecol* 2011; **117**: 663–671.
- Owen J, Hankins G, Iams JD *et al.* Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. *Am J Obstet Gynecol* 2009; **201**: e371–e378.
- Berghella V, Ludmir J, Simonazzi G, Owen J. Transvaginal cervical cerclage: evidence for perioperative management strategies. *Am J Obstet Gynecol* 2013; **209**: 181–192.
- DeFranco EA, Valent AM, Newman T, Regan J, Smith J, Muglia LJ. Adjunctive therapies to cerclage for the prevention of preterm birth: a systematic review. *Obstet Gynecol Int* 2013; **2013**: 528158.
- Berghella V, Rust OA, Althuisius SM. Short cervix on ultrasound: does indomethacin prevent preterm birth? *Am J Obstet Gynecol* 2006; **195**: 809–813.
- Jackson JR, Thorp J, Decesare J, Sang LM, Hernandez-Marin E, Gillis B. Safety of ibuprofen tocolysis. *Obstet Gynecol* 2014; **123**: 1495–1505.
- Richter ON, Dorn C, van de Vondel P, Ulrich U, Schmolling J. Tocolysis with atosiban: experience in the management of premature labor before 24 weeks of pregnancy. *Arch Gynecol Obstet* 2005; **272**: 26–30.
- Skupski DW, Lin SN, Reiss J, Eglinton GS. Extremely short cervix in the second trimester: bed rest or modified Shirodkar cerclage? *J Perinat Med* 2014; **42**: 55–59.
- Bollapragada SS, McLellan D, Anthony GS. Atosiban for prophylactic tocolysis following transabdominal cervico-isthmus cerclage. *J Obstet Gynaecol* 2006; **26**: 462–463.
- Summers JE, Moore ES, Ramsey CJ, Eggleston MK. Transabdominal cervical cerclage in triplet pregnancies and risk of extreme prematurity and neonatal loss. *J Obstet Gynaecol* 2011; **31**: 111–117.
- Boehm FH, Lombardi SJ, Rosemond RL. Immediate cerclage following delivery of one nonviable twin. A report of three cases. *J Reprod Med* 1992; **37**: 986–988.
- de Jong MW, van Lingen RA, Wildschut J, van Eijk J. Delayed interval delivery of two remaining fetuses in quintuplet pregnancy after embryo reduction: report and review of the literature. *Acta Genet Medica et Gemellol* 1992; **41**: 49–52.
- Jazayeri A, Mamlok V, Dorsett MM, Porter KB. Prolonged-interval delivery between the first and second twin. A case report. *J Reprod Med* 2002; **47**: 167–169.
- Althuisius SM, Dekker GA, Hummel P, van Geijn HP. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2003; **189**: 907–910.
- Berghella V, Prasertcharoensuk W, Cotter A, Rasanen J, Mittal S, Chaithong-wongwatthana S *et al.* Does indomethacin prevent preterm birth in women with cervical dilatation in the second trimester? *Am J Perinatol* 2009; **26**: 13–19.
- Conradt A, Weidinger H, Algayer H. Magnesium therapy decreased the rate of intrauterine fetal retardation, premature rupture of membranes and premature delivery in risk pregnancies treated with betamimetics. *Magnesium* 1985; **4**: 20–28.

- 19 Evans DJ, Kofinas AD, King K. Intraoperative amniocentesis and indomethacin treatment in the management of an immature pregnancy with completely dilated cervix. *Obstet Gynecol* 1992; **79**: 881–882.
- 20 Miller ES, Grobman WA, Fonseca L, Robinson BK. Indomethacin and antibiotics in examination-indicated cerclage: a randomized controlled trial. *Obstet Gynecol* 2014; **123**: 1311–1316.
- 21 Novy MJ, Gupta A, Wothe DD, Gupta S, Kennedy KA, Gravett MG. Cervical cerclage in the second trimester of pregnancy: a historical cohort study. *Am J Obstet Gynecol* 2001; **184**: 1447–1454 discussion 1454–1446.
- 22 Novy MJ, Haymond J, Nichols M. Shirodkar cerclage in a multifactorial approach to the patient with advanced cervical changes. *Am J Obstet Gynecol* 1990; **162**: 1412–1419 discussion 1419–1420.
- 23 Rust OA, Atlas RO, Jones KJ, Benham BN, Balducci J. A randomized trial of cerclage versus no cerclage among patients with ultrasonographically detected second-trimester preterm dilatation of the internal os. *Am J Obstet Gynecol* 2000; **183**: 830–835.
- 24 Rust OA, Atlas RO, Reed J, van Gaalen J, Balducci J. Revisiting the short cervix detected by transvaginal ultrasound in the second trimester: why cerclage therapy may not help. *Am J Obstet Gynecol* 2001; **185**: 1098–1105.
- 25 Ventolini G, Genrich TJ, Roth J, Neiger R. Pregnancy outcome after placement of 'rescue' Shirodkar cerclage. *J Perinatol* 2009; **29**: 276–279.
- 26 Leo L, Arduino S, Febo G *et al*. Cervical cerclage for malformed uterus. *Clin Exp Obstet Gynecol* 1997; **24**: 104–106.
- 27 Watanabe N, Suzuki T, Kitano E, Kitamura H, Hatanaka M, Sago H. Successful pregnancy in a patient suffering from recurrent mid-trimester miscarriage with C9 deficiency after receiving cervical cerclage followed by clindamycin and progesterone: a case report. *J Obstet Gynaecol Res* 2012; **38**: 562–566.
- 28 Kofinas A, Kofinas J. Indomethacin as a diagnostic and therapeutic tool in the management of progressive cervical shortening diagnosed by trans-vaginal sonography. *J Maternal-Fetal Neonatal Med* 2011; **24**: 79–85.
- 29 Locci M, Nazzaro G, Merenda A, Pisaturo ML, Lavisio P, Poppiti R *et al*. Atosiban vs ritodrine used prophylactically with cerclage in ICSI pregnancies to prevent preterm birth in women identified as being at high risk on the basis of transvaginal ultrasound scan. *J Obstet Gynaecol* 2006; **26**: 396–401.
- 30 Visintine J, Airolidi J, Berghella V. Indomethacin administration at the time of ultrasound-indicated cerclage: is there an association with a reduction in spontaneous preterm birth? *Am J Obstet Gynecol* 2008; **198**: e641–e643.
- 31 Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005; **106**: 181–189.
- 32 American College of O, Gynecologists. ACOG Practice Bulletin No.142: Cerclage for the management of cervical insufficiency. *Obstet Gynecol* 2014; **123**: 372–379.
- 33 Committee on Practice Bulletins-Obstetrics TACoO, Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012; **120**: 964–973.
- 34 Amin SB, Sinkin RA, Glantz JC. Metaanalysis of the effect of antenatal indomethacin on neonatal outcomes. *Am J Obstet Gynecol* 2007; **197**: e481–410.
- 35 Kamath-Rayne BD, Habli M, Rodriguez Z, Wu M, Gresh J, DeFranco EA. Antenatal exposure to sulindac and risk of necrotizing enterocolitis. *Am J Obstet Gynecol* 2015; **212**: e1–e7.
- 36 Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI. Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993; **329**: 1602–1607.