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Indomethacin as a diagnostic and therapeutic tool in the management of progressive cervical shortening diagnosed by trans-vaginal sonography

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Abstract

Objective. To evaluate the role of indomethacin in discriminating between preterm labour and cervical insufficiency-related cervical shortening.

Methods. Retrospective analysis of all cases of cervical shortening on singleton gestations. All patients were treated according to our protocol with one or more of the following three modalities: (1) bed rest only, (2) bed rest and indomethacin and (3) cervical cerclage, bed rest, and indomethacin. Outcomes: foetal loss <24 weeks, birth weight, delivery <34 weeks, and delivery <37 weeks.

Results. We treated 342 patients: 167 (48.8%) with bed rest only, 21 (6.1%) with cerclage, and 154 (45.1%) with indomethacin. By 28 weeks 56 (16.3%) remained stable or improved with bed rest only, 91 (26.6%) failed indomethacin and required cerclage, and the remaining 173 (50.6%) responded well to indomethacin and nifedipine. Birth weight was 3119 g $\pm$ 651 (SD) and GA at delivery 37.4 weeks $\pm$ 2.5 (SD). Of the 342 patients, 4 (1.2%) aborted <24 weeks, 1 was terminated (achondroplasia), 320 (93.6%) patients delivered >34 weeks and 301 (88.1%) >37 weeks.

Conclusions. Use of indomethacin in patients with cervical shortening discriminates patients with cervical insufficiency from those in premature labour and improves outcomes in comparison to existing published reports.

Keywords: *Cervix, pregnancy, preterm, cerclage, indomethacin*

Introduction

Cervical insufficiency has been defined as recurrent second trimester pregnancy loss in the absence of labour [1]. The introduction of ultrasound has added a new dimension in the definition of cervical insufficiency [2]. A number of surgical techniques [3,4] are used for the treatment of cervical insufficiency. Cervical cerclage is the treatment of choice for patients with cervical insufficiency, despite the fact that the subject remains controversial and several studies have failed to prove any benefit from cerclage placement in patients with history or ultrasound findings suggestive of cervical insufficiency [5–7].

The addition of ultrasound [8,9] in the diagnosis and management of patients with known or suspected cervical insufficiency has improved our understanding of the relationship of cervical physiology and preterm delivery. Cervical insufficiency usually coexists with preterm labour and it has been proposed that the two are part of the same continuum [10]. Patients undergoing cervical cerclage after cervical changes diagnosed by ultrasound may do as well as patients undergoing elective cerclage based on strong history of pregnancy loss because of cervical insufficiency [11,12]. There is increasing evidence that inflammation is a common coexisting factor in patients with cervical insufficiency and/or preterm labour [13–17].

Indomethacin and nifedipine were found to be efficacious and safe tocolytic agents with significant prolongation of pregnancy in comparison to beta-mimetics and magnesium sulphate [18–20]. In our practice we have used indomethacin for tocolysis in some patients with short cervix documented with transvaginal ultrasound, and preterm labour since 1995. Over the years we noticed that some patients responded to indomethacin with complete restoration of cervical length and some did not. Patients not

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responding to indomethacin were more likely to do well with cerclage and those responding to indomethacin were more likely to do well with tocolysis and bed rest. Considering the risks, the lack of efficacy as well as the cost of magnesium sulphate tocolysis, [21] we developed a protocol for the use of indomethacin and calcium channel blocker nifedipine for the management of premature cervical shortening documented by trans-vaginal ultrasonography.

This retrospective cohort study was designed to evaluate the role of indomethacin as a therapeutic agent as well as a diagnostic tool to discriminate preterm labour from isolated cervical insufficiency in patients with ultrasonically documented progressive premature cervical shortening.

Methods

We reviewed the medical records of all patients treated at Kofinas Perinatal, New York Methodist Hospital, Brooklyn, New York from January 1st 2002 to June 30th 2008. The study was approved by the institution's IRB. We identified patients by means of electronic search of our ultrasound-reporting database for all patients with evidence of cervical shortening. Exclusion criteria included the following if present at the time of diagnosis of cervical shortening: multiple gestations, foetal anomalies, oligohydramnios, premature rupture of membranes (PROM), growth restriction ($<$10th per cent for gestation), gestational age $>$32 weeks, and active vaginal bleeding during the first cervical assessment. Neonatal outcomes were extracted from the neonatal hospital record. Outcome parameters included pregnancy loss before 24 completed weeks, birth weight at delivery, delivery prior to 34 completed weeks, delivery prior to 37 completed weeks, oligohydramnios, foetal demise after 24 weeks, premature closure of ductus arteriosus, and neonatal death. Three hundred and forty-two patients met the inclusion criteria.

The indications for cervical evaluation are given on Table I. Cervical measurements were obtained by means of transvaginal sonography and the following parameters were evaluated: total cervical length from the external to the functional internal cervical os and the presence of funneling. The shortest functional length was used [22,23]. However, the decision for treatment was only based on cervical length. The presence or absence of funneling was recorded but not used in the treatment decision since its value is still not clear [24,25]. Cervical shortening was classified as mild if the cervix was between 26 and 34 mm, moderate when the cervix was between 15 and 25 mm and severe when it was $<$15 mm. The first line of treatment for the mild group was bed rest only for 1 week, for the moderate group it was bed rest with indomethacin 50 mg every 6 h for 1 week and for the severe group it was cervical cerclage with bed rest and indomethacin 50 mg every 6 h for 1 week. All patients were followed weekly for the next 4 weeks until cervical length stability was achieved and the patients were symptom free. On the first follow-up visit the cervix was measured and the patient was managed according to results of first treatment. In the bed rest only group if the cervix remained stable or improved, we continued the same treatment until 4 weeks of stability. Subsequently the patient returned to normal activity and the cervix was evaluated after 1 week of normal activity. If the cervix remained stable the patient was released to standard obstetrical care and if the cervix declined, the patient was treated according to cervical length. In the indomethacin group, if the cervix remained stable or improved after the initial 7-day course of indomethacin, patients were started on nifedipine XL 60 mg every 12 h. After 1 week of nifedipine if the cervix dropped below 25 mm during the follow-up period, a brief course of indomethacin 50 mg every 6 h was used for 48 h in addition to nifedipine. This scheme was repeated as necessary up to 32 weeks gestation. Indomethacin was never used after 32 weeks gestation. Failure to respond to the combination of nifedipine/indomethacin with further deterioration of cervical length to $<$26 mm constituted indication for cerclage placement. Nifedipine was used until 37 weeks in patients whose cervix remained between 25 mm and 34 mm. However, the dosage was gradually tapered to the lowest that maintained cervical stability at $>$25 mm. Patients treated with indomethacin underwent amniotic fluid volume and foetal ductus arteriosus Doppler assessment prior to the initiation of treatment and at the completion of indomethacin treatment. For the statistical analysis we only used the data from the first 7-day indomethacin course since this represents the highest level of foetal exposure to indomethacin (Figure 1). All patients were educated in person and with additional written material regarding the symptoms and signs of preterm birth. Patients were educated

Table I. Indications for cervical evaluation.

Indication for ultrasound	Number of patients	Per cent of total
Pregnancy by ART	109	31.8
History of foetal demise $>$20 weeks	28	8.2
History of preterm birth	56	16.3
History of preterm labour	36	10.5
Recurrent pregnancy loss $<$12 weeks	38	11.1
Recurrent pregnancy loss $>$12 weeks	39	11.4
Current preterm labour symptoms*	36	10.5

ART, assisted reproductive technologies.
*Intermittent lower abdominal pain, cramps, pelvic pressure, intermittent lower back pain.

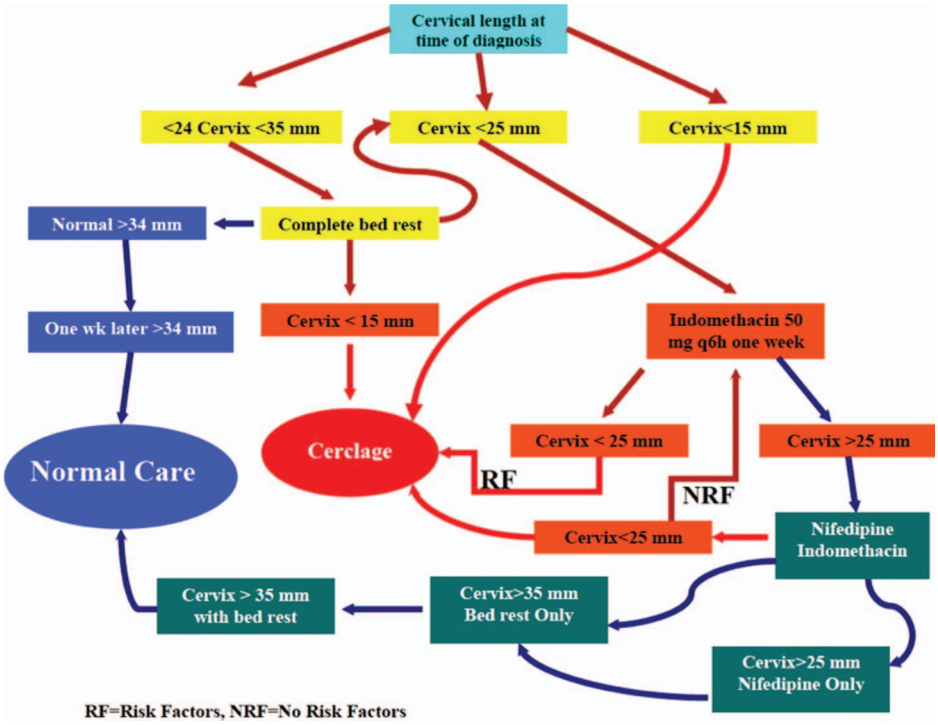

Figure 1. Flow chart for the management of patients with progressively short cervix. Risk factors: history of second trimester loss or history of preterm birth.

on the risks of preterm labour, preterm birth, the benefits and risks of the treatment and the possible maternal and foetal side effects. In addition, all patients had direct access to the principal author (AK) 24/7 and were instructed to call whenever they thought that something was wrong in relation to the following symptoms: pelvic pressure, feeling of stretching and pulling in the pelvis, low back pain (in the region of the tail-bone), pressure in the vagina, excessive discharge (feeling wet in the vagina), feeling of menstrual cramping, intermittent deep pelvic discomfort, gas pains and rectal pressure and feeling of constipation. In addition, patients were instructed to call for any other concern that they might have regarding treatment related side effects.

We used the Macdonald type of cerclage. We employed two sutures of #2 Merselene threaded on a #4 half-tapered Mayo atraumatic needle. We found this needle to be of superior quality in terms of strength, atraumatic and yet very sharp, and easy to manoeuvre in the narrow confines of the vaginal vault. We always place two sutures; the second one is usually placed 1 cm above the first one. The cerclage placement was performed only when medical treatment failed and the diagnosis of cervical insufficiency was made. Gestational age ranged from 12 weeks to 28 weeks. We found over the years that the arbitrary cut-off point of 24 weeks for cerclage placement is not clinically or ethically justifiable just because a foetus has a 50% chance to survive. Technically, there is no difference between 24 and 28 weeks and the limited procedure-related risks were not different. In one patient, amniocentesis was performed at 22 weeks for amnioreduction in order to restore the hour-glassing amniotic sac with the assistance of a Foley catheter after the amnioreduction. This patient experienced a failed elective cerclage placed at a different institution prior to her visit with us.

We performed statistical analysis by means of JMP Statistical Discovery Software for personal computers (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513), and analysed the data by one-way analysis of variance and χ^2-test when appropriate. Power analysis revealed that the study sample is enough to provide 80% power in identifying the following differences with an $\alpha < 0.05$: 1 week difference in gestational age, 150 g difference in birth weight, and 5% difference in the frequency of the outcomes analysed.

Results

At the time of diagnosis, mean gestational age for the entire group was 20.4 ± 4.9 (SD) weeks and there was no difference between the mild, moderate, and severe cervical shortening subgroups ($P = 0.26$). Mean $\pm$ (SD) cervical length at the time of diagnosis was 25 ± 6.8 mm but there were significant differences among the three severity groups. Mean cervical length in the mild group was 30.3 ± 4.2 mm, in the moderate group was 21.5 ± 3.9 mm, and the severe group was 8.6 ± 4 mm ($P < 0.001$).

Of the 342 patients with short cervix at the time of diagnosis, 167 (48.9%) were treated with bed rest only. In these patients mean cervical length at diagnosis was 30.3 mm and after 1 week bed rest mean cervical length remained essentially unchanged at 30 mm (P = ns). However, after 1 week of bed rest, the cervix improved in 63 patients, deteriorated in 67 and remained unchanged in 37.

One hundred and fifty-four patients in the moderate group (45% of total) were treated with indomethacin and bed rest for 1 week. In these patients mean cervical length at diagnosis was 21.5 mm and after 1 week of treatment mean cervical length increased to 31.8 mm ($P < 0.001$). In this group after 1 week of treatment with indomethacin 15 patients deteriorated and received cerclage, 12 remained unchanged, and 127 improved.

Twenty-one patients (6.1%) were treated with cerclage and indomethacin at the time of diagnosis. In these patients mean cervical length at diagnosis was 8.6 mm and after cerclage placement and 1 week of treatment with indomethacin the cervix improved to 37.5 mm ($P < 0.001$). In the cerclage group after 1 week of treatment with indomethacin, 20 improved and one deteriorated.

By 28 weeks gestation, only 56 (16.3%) of the patients remained stable or improved with bed rest alone; these patients returned to normal obstetric care. From the group of patients treated with tocolysis and bed rest, 92 (26.8%) patients failed tocolysis and required cerclage. In total 113 (33.1%) of the patients were treated with cerclage, and the remaining 173 (50.6%) responded well to indomethacin and nifedipine maintenance (Table II).

Mean birth weight of the entire study sample was 3119 g $\pm$ 651 (SD) and GA at delivery 37.4 weeks $\pm$ 2.5 (SD). The mild and moderate groups had similar mean birth weights but the severe group had significantly lower mean birth weight ($P < 0.002$). These differences were most likely the result of shorter mean gestational age in the severe group compared with the mild and moderate groups ($P < 0.001$). Of the 342 patients 4 (1.2%) experienced PROM and spontaneous abortion prior to 24 weeks, one was diagnosed with thanatophoric dwarfism 2 weeks after the onset of treatment and terminated the pregnancy electively at 23 weeks and one was lost to follow-up after 25 weeks. Of the 342 study subjects, 7(2%) delivered live-born neonates between 23 and 28 completed weeks, 328 (95.9%) delivered after 32 completed weeks, 320 (93.6%) of the patients delivered after 34 weeks and 301 (88.1%) after 37 weeks.

Funneling is associated with certain significant differences in this study. The presence of funneling is associated with increased risk for cerclage, and decreased response to bed rest and tocolytic treatment (Table III). In addition, the presence of funneling is associated with earlier gestation and shorter cervical length at diagnosis (Table IV). Furthermore, the presence of funneling was associated with more foetuses born prior to 34 weeks as well as prior to 37 weeks (Table V).

Table II. Progressive changes in the treatment modality from the time of diagnosis (first visit) to 28 weeks gestation.

Time of treatment	BR, %	I/N, %	C, %
Visit no. 1	48.8	45.1	6.1
Visit no. 2	26.4	54.2	19.4
Visit no. 3	21.4	51.2	27.3
Visit no. 4	18.2	50.1	31.7
28 weeks	16.3	50.6	33.1

BR, bed rest only; I/N, bed rest with indomethacin and nifedipine maintenance; C, bed rest, cerclage, indomethacin and nifedipine maintenance as needed.
After visit no. 4 and by 28 weeks gestation most patients remained in their respective category.

Table III. Final treatment modality according to the presence of cervical funneling.

	Treatment modality			
Funneling (n)	BR (%)	I/N (%)	C (%)	P*
Absent (210)	49 (23.3)	142 (67.6)	19 (9.1)	0.001
Present (132)	7 (5.3)	31 (23.5)	94 (71.2)	0.001

BR, bed rest only; I/N, bed rest with combination of indomethacin and nifedipine as needed; C, cerclage with bed rest and I/N tocolysis as needed.
*Chi square analysis.

Table IV. Gestational age and cervical length at the time of diagnosis according to the presence of funneling.

	Funneling		
	Absent	Present	P*
Cervical length (mm)	26.4 $\pm$ 3.9	22 $\pm$ 4.1	<0.001
Gestational age (weeks)	21.4 $\pm$ 4.9	18.8 $\pm$ 4.8	<0.001

Values are in mean $\pm$ SD.
*Chi square analysis.

Table V. Gestational age at time of delivery according to the presence of funneling at the time of diagnosis.

	Funneling		
Gestational age at delivery	Absent, $n=210$ (%)	Present, $n=132$ (%)	P*
GA <34 weeks	1 (0.5)	15 (11.4)	<0.0001
GA <37 weeks	11 (5.2)	24 (18.2)	<0.003

*Chi square analysis.

None of the foetuses experienced evidence of ductal constriction of any clinical degree since none of the foetuses exhibited abnormal ductus arteriosus PI values of <1.9 after 7 days of indomethacin [26]. Of the 173 patients that received indomethacin, only 50 (29%) experienced a mild decline in the amniotic fluid volume but only 17 (9.8%) patients experienced transient clinical oligohydramnios at the completion of 7 day indomethacin course. In all cases the amniotic fluid returned to pretreatment levels within 3–7 days after indomethacin was stopped.

Pregnancy was prolonged from the time of diagnosis for an average of 16.4 weeks. Comparison of gestational age prolongation according to the final treatment revealed significant differences in the three treatment modalities. When we analysed the data according to the final treatment employed, cerclage was found to be the most successful in prolonging the pregnancy by a mean 18.3 weeks. In contrast, bed rest alone when successful, prolonged pregnancy by a mean of 15.3 weeks and tocolysis prolonged the pregnancy by 16.2 weeks (Table VI).

Because 31.8% of our patients conceived by means of assisted reproduction, we were concerned that this group may be intrinsically different than the rest of the patients. For this reason, we compared the findings of this group against all the other indication-related groups for the following parameters: gestational age at time of diagnosis, initial cervical length, response to indomethacin, birth weight, gestational age at delivery, delivery <34 and <37 weeks and we found no differences. Therefore, it was appropriate to then evaluate the entire study sample as one group with similar characteristics.

Maternal side effects from indomethacin consisted of gastrointestinal irritability, headache, and water retention as evident by lower extremity oedema. Maternal side effects from nifedipine consisted of headache in the form of light-headedness, erythema of the lower extremities in upright position (capillary and venous dilatation), palpitations and weakness. These symptoms subsided or were easily tolerated by the patients after reassuring communications with the principal investigator. All patients completed the treatment although in a few instances dosage modification became necessary due to maternal side effects. In no case treatment was withheld due to foetal side effects.

Table VI. Comparison of pregnancy prolongation according to the final treatment modality employed.

Treatment modality	Number of patients	Weeks mean	Weeks SD	*P**
B	56	15.3	5.2	0.0005
C	113	18.3	5.5	
I/N	173	16.2	5.5	

B, bed rest only; C, bed rest, I/N tocolysis and cerclage; I/N, indomethacin and nifedipine maintenance along with bed rest.
*One-way analysis of variance, comparison of all three pairs was performed by Tukey–Kramer of *post hoc* analysis.

Discussion

This is a study that describes the clinical outcomes produced by the application of a specific protocol for the treatment of patients with progressive premature cervical shortening documented with trans-vaginal ultrasound. We understand the limitations of such a report. Our study is based on clinical observation over several years in managing patients with short cervix with *subclinical* premature labour and/or insufficient cervix. Prior to 2001, such patients were managed with various methods over the years including but not limited to hospitalisation and tocolysis with either $MgSO_4$ or beta-agonists or nifedipine or indomethacin and at times various combinations of the above. During those earlier years we noted that patients treated with indomethacin responded differently than the other tocolytics. Specifically, when the cervical length increased with indomethacin treatment the patient did better with tocolysis alone. When the cervix did not improve or deteriorated after a course of indomethacin, the patient was more likely to require a cerclage. Such patients delivered at an earlier gestation also. Based on such observations that were internally analysed (clinical and statistical analysis as part of our quality assurance process) we created the protocol described in this report. Since then, we treated all patients with short cervix strictly according to this protocol.

Stratification according to degree of cervical shortening permitted us to employ treatments of variable degrees in various groups. This protocol affords the gradual elimination of the aetiologies that may be associated with progressive premature cervical shortening other than cervical insufficiency, leading to the most appropriate diagnosis. Only one-third of the patients with progressive cervical shortening, required cerclage treatment. The largest portion of cerclages (80%) was placed in patients that failed tocolysis. Although bed rest has never shown to prevent prematurity, our findings justify its use in patients with cervical shortening since 16% of such patients returned to normal state after one or more weeks of bed rest. Treating patients with progressive cervical shortening for the specific cause helped us achieve results that are better than related outcomes from similar patients that were not treated with a specific protocol or were not treated at all. Fox et al., reported significantly higher rates of prematurity in similar patients with progressive cervical shortening; 60% of the patients in their study

delivered <37 weeks and 28% of the patients delivered <34 weeks [27]. Both studies were performed in New York City at similar times with similar populations to the best of our knowledge. We realise the limitation of not having our internal controls, but comparison of our outcomes to those of Fox et al. [27], clearly indicate that there might exist a real difference because of our protocol. Even if there are some unknown differences between the study samples of the two studies, we believe that it might not be inappropriate to use Fox's et al. [27] study as a control to our outcomes. If one were to compare our outcomes with previous studies that did not take a stepwise approach but treated the patients either with cerclage or tocolysis, one would find that our approach has the potential to deliver improved outcomes. Of course, such a claim would be more valid if our protocol were tried under the circumstances of a randomised clinical trial. In a private practice setting this was not possible. Our practice is primarily dealing with patients who have infertility or experienced poor obstetrical outcomes before and came to us for treatment not willing to be part of a study.

The benefit of cervical cerclage in the treatment of the short cervix remains controversial [5,12,28–30]. One of the reasons for such controversy might be the lack of standardised diagnostic criteria. This leads to the use of cerclage in patients who may or may not have cervical insufficiency; this may cause unintended consequences [31]. Serial follow-up with vaginal sonography is a medically acceptable alternative to the use of elective cerclage [12]. This has significant implications since a significant number of patients have histories that are not clear as to the aetiology of the pregnancy loss. In a recent multicentre randomised clinical trial in women with a prior spontaneous preterm birth <34 weeks and cervical length <25 mm, cerclage reduced previable birth and perinatal mortality but did not prevent birth <35 weeks, unless cervical length was <15 mm [32]. Although many or our patients fall in this category, many more are not. However, all of our patients had risk factors related to preterm birth and poor perinatal outcomes.

In the past, cervical insufficiency and preterm labour were seen as mutually exclusive. However, there has been significant evidence that disputes this concept [10,22]. Instead, of a dichotomous state, there is a continuum and pregnancy loss in the second trimester may not be the result of either 'pure' cervical insufficiency or 'pure' preterm labour. This dichotomy has led to a management duality where labour was a contraindication to placing a cerclage and patients would be treated with either cerclage placement or tocolysis. In our experience, most of the patients identified with progressive premature cervical shortening when properly questioned, reported vague symptoms (vaginal and rectal pressure, menstrual cramping like pain, wetness in the vagina and lower back pain) for several days before the diagnosis. Early recognition of such symptoms should prompt evaluation of the cervix with transvaginal sonography. Failure to act on such symptoms may lead to delayed diagnosis of cervical insufficiency and/or preterm labour.

Funneling has been a controversial subject with conflicting findings regarding its impact on prematurity as an independent factor [24]. We found significant associations between the presence of funneling and severity of cervical weakness as defined by increased need for cerclage. In addition, we found significant associations between the presence of funneling and prematurity before 34 as well before 37 weeks gestation. These findings are in agreement with *one other published report* [33]. Our findings suggest that cervical shortening with funneling is more likely to be associated with inherent structural cervical weakness. In contrast, cervical shortening in the absence of funneling is more likely to be associated with external forces (contractility) that respond favourably to tocolysis.

In summary, this study demonstrates for the first time the benefit of the use of indomethacin as a diagnostic and therapeutic tool. The use of indomethacin *in patients with progressive cervical shortening* seems to improve cervical length significantly and reduce the need for cerclage placement to only 33% of patients with short cervix. The significant prolongation of gestation in pregnancies with progressively shortening cervix is an important clinical improvement considering that the protocol has achieved a prolongation of gestational age beyond 34 weeks in 94% of patients who were diagnosed with progressively shorter cervix between 12 and 28 weeks gestation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Easterday CL, Reid DE. The incompetent cervix in repetitive abortion and premature labor. N Engl J Med 1959;260:687–690.
2. Feingold M, Brook I, Zakut H. Detection of cervical incompetence by ultrasound. Acta Obstet Gynecol Scand 1984;63:407–410.
3. McDonald I. Suture of the cervix for inevitable miscarriage. J Obstet Gynaecol Br Commonw 1957;64:346.
4. Shirodkar V. A new method of operative treatment for habitual abortion in the second trimester of pregnancy. Antiseptic 1955;52:299.
5. Berghella VO, To AO, Rust MS, Althuisius OA. Cerclage for short cervix on ultrasonography: meta-analysis of trials using

individual patient-level data. Obstet Gynecol 2005;106:181–189.
6. Berghella V, Tolosa AO. Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial. Am J Obstet Gynecol 2004;191:1311–1317.
7. Althuisius SMD, Hummel GA, van Geijn P. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. Am J Obstet Gynecol 2003;189:907–910.
8. Guzman ERV, McLean AM, Martins DA, Benito ME, Hanley CW. The natural history of a positive response to transfundal pressure in women at risk for cervical incompetence. Am J Obstet Gynecol 1997;176:634–638.
9. Chung TKH, Kong CJ, Woo D, Rogers WK. Transvaginal sonography in the diagnosis and management of cervical incompetence. Gynecol Obstet Invest 1993;36:59–61.
10. Iams JD, Johnson FF, Sonek J, Sachs L, Gebauer C, Samuels P. Cervical competence as a continuum: a study of ultrasonographic cervical length and obstetric performance. Am J Obstet Gynecol 1995;172:1097.
11. Kurup M. Cervical incompetence: elective, emergent, or urgent cerclage. Am J Obstet Gynecol 1999;181:240–246.
12. Guzman ERF, Vintzileos JK, Ananth AM, Walters CV, Gipson C. Pregnancy outcomes in women treated with elective *versus* ultrasound – indicated cervical cerclage [see comments]. Ultrasound Obstet Gynecol 1998;12:323–327.
13. Dudley DJ. Immunoendocrinology of preterm labor: the link between corticotropin-releasing hormone and inflammation. Am J Obstet Gynecol 1999;180 (1 Pt 3):S251–S256.
14. Gross G, et al. Inhibition of cyclooxygenase-2 prevents inflammation-mediated preterm labor in the mouse. Am J Physiol Regul Integr Comp Physiol 2000;278:R1415–R1423.
15. Holst RMM-B, Wennerholm I, Hagberg UB, Jacobsson H. Interleukin-6 and interleukin-8 in cervical fluid in a population of Swedish women in preterm labor: relationship to microbial invasion of the amniotic fluid, intra-amniotic inflammation, and preterm delivery. Acta Obstet Gynecol Scand 2005;84:551–557.
16. Sakai MS, Yoneda Y, Kasahara S, Arai T, Okada T, Hosokawa M, Kato H, Soeda K, Saito Y. Elevated interleukin-8 in cervical mucus as an indicator for treatment to prevent premature birth and preterm, pre-labor rupture of membranes: a prospective study. Am J Reprod Immunol 2004;51:220–225.
17. Sakai MS, Tabata A, Sasaki M, Yoneda Y, Arai S, Kato T, Yamakawa K, Saito Y. Evaluation of effectiveness of prophylactic cerclage of a short cervix according to interleukin-8 in cervical mucus. Am J Obstet Gynecol 2006;194:14–19.
18. Vermillion ST, Landen CN. Prostaglandin inhibitors as tocolytic agents. Semin Perinatol 2001;25:256–262.
19. Larmon JER, May BS, Dickerson WL, Fischer GA, Morrison RG. Oral nicardipine versus intravenous magnesium sulfate for the treatment of preterm labor. Am J Obstet Gynecol 1999;181:1432–1437.
20. King JF, Cole V, Thornton S. Calcium channel blockers for inhibiting preterm labor. Cochrane Database Syst Rev 2003;Art. no.: CD002255(1):1–50.
21. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour (Review). Cochrane Database Syst Rev 2002;Art. no.: CD00 1060(4):1–106.
22. Iams JDG, Meis RL, Mercer PJ, Moawad BM, Das A, Thom A, McNellis E, Copper D, Johnson RL, Roberts F. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network [see comments]. N Engl J Med 1996;334:567–572.
23. Yost NPB, Twickler SL, Leveno DM. Pitfalls in ultrasonic cervical length measurement for predicting preterm birth. Obstet Gynecol 1999;93:510–516.
24. Berghella VO, MacPherson J, Yost C, Swain N, Dildy M, 3rd Miodovnik GA, Langer M, Sibai O. Natural history of cervical funneling in women at high risk for spontaneous preterm birth. Obstet Gynecol 2007;109:863–869.
25. To MSS, Liao C, Cacho AW, Nicolaides A. Cervical length and funneling at 23 weeks of gestation in the prediction of spontaneous early preterm delivery. Ultrasound Obstet Gynecol 2001;18:200–203.
26. Respondek M, Weil SR, Huhta JC. Fetal echocardiography during indomethacin treatment. Ultrasound Obstet Gynecol 1995:86–89.
27. Fox NJ-P, Predanic C, Chasen M. Short cervix: is follow-up measurement useful? Ultrasound Obstet Gynecol 2007;29: 44–46.
28. Althuisius SMD, Hummel GA, Bekedam P, van Geijn DJ, HP. Final results of the cervical incompetence prevention randomized cerclage trial (CIPRACT): therapeutic cerclage with bed rest *versus* bed rest alone. Am J Obstet Gynecol 2001;185:1106–1112.
29. Belej-Rak TO, Windrim N, Ross R, Hannah S. Effectiveness of cervical cerclage for a sonographically shortened cervix: a systematic review and meta-analysis. Am J Obstet Gynecol 2003;189:1679–1687.
30. Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. Cochrane Database Syst Rev 2003;(1):CD003253.
31. Romero RE, Erez J, Hassan OS. The role of cervical cerclage in obstetric practice: can the patient who could benefit from this procedure be identified? Am J Obstet Gynecol 2006;194:1–9.
32. Owen J, Hankins G, Iams JD, Berghella V, Sheffield JS, Perez-Delboy A, Egerman RS, Wing DA, Tomlinson M, Silver R, Ramin SM, Guzman ER, Gordon M, How HY, Knudtson EJ, Szychowski JM, Cliver S, Hauth JC. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. Am J Obstet Gynecol 2009;201:375.e1–375.e8.
33. Rust OA, Kimmel RO, Roberts S, Hess WE. Does the presence of funnel increase the risk of adverse perinatal outcome in a patient with a short cervix? Am J Obstet Gynecol 2005;192:1060–1066.