UNIVERSITÀ DEGLI STUDI
DI PADOVA

AZIENDA OSPEDALIERA
DI PADOVA

Dipartimento di Salute della Donna e del Bambino
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PESSARIO CERVICALE NELLA PREVENZIONE DEL PARTO PRETERMINE

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DEFINING THE PROBLEM ….

IL PARTO PRETERMINE (PPT)

- ✓ Complica dal 6 al 10% delle gravidanze nei paesi industrializzati e fino al 18% delle gravidanze in alcuni Stati Africani

  15 milioni l'anno, di cui 13 milioni in Asia e Africa

- ✓ E' la principale causa di mortalità e morbidità perinatale nel mondo

Quasi 1 milione di bambini l'anno muoiono per complicazioni

- ✓ Nei Paesi industrializzati, il 10% delle spese destinate alla cura dei bambini è derivato da problematiche connesse al parto pretermine

Lumley et al 2003; Ngoc et al 2006;
Laws et al 2005; Lewitt et al 1995;
Arabin et al 2003

DEFINING THE PROBLEM ….

FATTORI DI RISCHIO PER PARTO PRETERMINE

Origine multifattoriale

- ✓ Storia di pregresso parto pretermine è il fattore di rischio principale e più importante

Tasso di ricorrenza di PPT è del
- *22,5% se un pregresso PPT*
- *32% se due pregressi PPT*

Le donne che hanno partorito tra 20-31 sg, nel 29,3% dei casi partoriranno < 37 sg e nel 10% il parto sarà ad un'età gestazionale simile al precedente

- ✓ Il riscontro di cervicometria ridotta (< 25 mm) prima delle 28 sg è predittore di rischio per PPT spontaneo prima delle 34 sg sia nelle gravidanze singole che gemellari
- ✓ Gravidanza gemellare

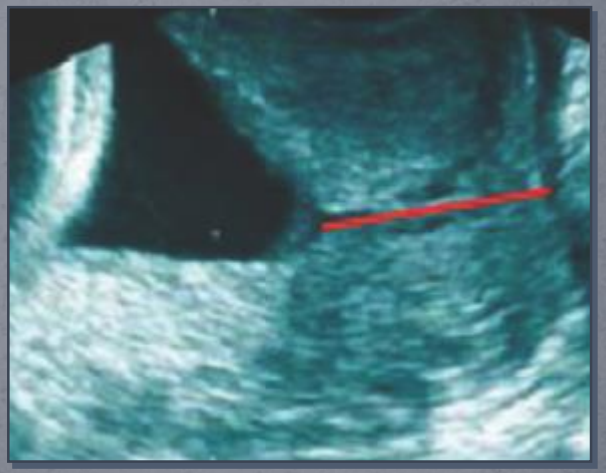
Più del 50% delle gravidanze gemellari partoriranno prima delle 37 sg.
Il rischio di PPT per le trigemellari è del 97%

Dodd et al, 2013

DEFINING THE PROBLEM ….

QUALE PREVENZIONE?

- ✓ Nei Paesi Industrializzati, la minaccia di parto pretermine è il motivo più comune di ricovero durante la gravidanza
- ✓ L'obiettivo di ridurre il tasso di PPT e di ospedalizzazione prevede la prevenzione del PPT non solo nelle pazienti con storia di PPT (10%), ma anche in quelle con riscontro incidentale di cervicometria ridotta (40%)
- ✓ L'ecografia TV eseguita nel II trimestre per misurare la cervicometria può identificare pazienti asintomatiche con cervicometria ridotta che risultano ad alto rischio di PPT
- ✓ Di conseguenza, è attualmente in rivalutazione il ruolo di metodiche di prevenzione secondaria come progesterone, cerchiaggio e pessario cervicale



Falcao V et al, 2016

MANAGEMENT STRATEGIES

PROGESTERONE

✓ DONNE CON STORIA DI PREGRESSO PARTO PRETERMINE

Riduzione di:

- PPT < 34 e 37 sg (RR 0,31 e 0,55)
- rischio di morte perinatale (RR 0,50)
- Peso fetale alla nascita < 2500 g (RR 0,58)
- Enterocolite necrotizzante (RR 0,40), uso di ventilazione assistita (RR 0,30) e ricovero in patologia neonatale (RR 0,24)
- Morte neonatale (RR 0,45)

} Riduzione di mortalità perinatale e neonatale

✓ DONNE CON RISCONTRO DI CERVICOMETRIA RIDOTTA

- Riduzione di rischio di PPT < 34 e 28 sg (RR 0,64 e 0,59)
- Aumentato rischio di orticaria (RR 5,03)
- NON effetti su mortalità perinatale e neonatale

✓ GRAVIDANZE GEMELLARI

- Non riduzione statisticamente significativa in morte perinatale o rischio di PPT

✓ DONNE CON MINACCIA DI PARTO PRETERMINE E ALTRI FR PER PPT

- Riduzione del rischio di peso fetale alla nascita < 2500 g (RR 0,52 e 0,48)

Dodd et all, 2013

PROGESTERONE

Lancet. 2016 May 21;387(10033):2106-16. doi: 10.1016/S0140-6736(16)00350-0. Epub 2016 Feb 24.

Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial

Jane Elizabeth Norman, Neil Marlow, Claudia-Martina Messow, Andrew Shennan, Phillip R Bennett, Steven Thornton, Stephen C Robson, Alex McConnachie, Stavros Petrou, Neil J Sebire, Tina Lavender, Sonia Whyte, John Norrie, for the OPPTIMUM study group

Abstract

BACKGROUND: Progesterone administration has been shown to reduce the risk of preterm birth and neonatal morbidity in women at high risk, but there is uncertainty about longer term effects on the child.

METHODS: We did a double-blind, randomised, placebo-controlled trial of vaginal progesterone, 200 mg daily taken from 22-24 to 34 weeks of gestation, on pregnancy and infant outcomes in women at risk of preterm birth (because of previous spontaneous birth at ≤34 weeks and 0 days of gestation, or a cervical length ≤25 mm, or because of a positive fetal fibronectin test combined with other clinical risk factors for preterm birth [any one of a history in a previous pregnancy of preterm birth, second trimester loss, preterm premature fetal membrane rupture, or a history of a cervical procedure to treat abnormal smears]). The objective of the study was to determine whether vaginal progesterone prophylaxis given to reduce the risk of preterm birth affects neonatal and childhood outcomes. We defined three primary outcomes: fetal death or birth before 34 weeks and 0 days gestation (obstetric), a composite of death, brain injury, or bronchopulmonary dysplasia (neonatal), and a standardised cognitive score at 2 years of age (childhood), imputing values for deaths. Randomisation was done through a web portal, with participants, investigators, and others involved in giving the intervention, assessing outcomes, or analysing data masked to treatment allocation until the end of the study. Analysis was by intention to treat. This trial is registered at ISRCTN.com, number ISRCTN14568373.

FINDINGS: Between Feb 2, 2009, and April 12, 2013, we randomly assigned 1228 women to the placebo group (n=610) and the progesterone group (n=618). In the placebo group, data from 597, 587, and 439 women or babies were available for analysis of obstetric, neonatal, and childhood outcomes, respectively; in the progesterone group the corresponding numbers were 600, 589, and 430. After correction for multiple outcomes, progesterone had no significant effect on the primary obstetric outcome (odds ratio adjusted for multiple comparisons [OR] 0·86, 95% CI 0·61-1·22) or neonatal outcome (OR 0·62, 0·38-1·03), nor on the childhood outcome (cognitive score, progesterone group vs placebo group, 97·3 [SD 17·9] vs 97·7 [17·5]; difference in means -0·48, 95% CI -2·77 to 1·81). Maternal or child serious adverse events were reported in 70 (11%) of 610 patients in the placebo group and 59 (10%) of 616 patients in the progesterone group (p=0·27).

INTERPRETATION: Vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long-term benefit or harm on outcomes in children at 2 years of age.

	Placebo group	Progesterone group	Unadjusted odds ratio (95% CI) or difference in means (95% CI)	p value (unadjusted)	Adjusted odds ratio (95% CI)* or difference in means (95% CI)	p value (adjusted*)
Fetal death or delivery <34 weeks of gestation	108/597 (18%)	96/600 (16%)	0·86 (0·64 to 1·17)	0·34	0·86 (0·61 to 1·22)	0·67
Neonatal morbidity or death	60/587 (10%)	39/589 (7%)	0·62 (0·41 to 0·94)	0·02	0·62 (0·38 to 1·03)	0·072
Cognitive composite score at 2 years†‡	97·7 (17·5)	97·3 (17·9)	−0·48 (−2·77 to 1·81)§	0·68	−0·48 (−2·77 to 1·81)§	0·68
Components of the obstetric outcome						
Fetal death	7/597 (1%)	8/600 (1%)	1·14 (0·41 to 3·17)	0·8	..	..
Liveborn delivery before 34 weeks	101/590 (17%)	88/592 (15%)	0·85 (0·62 to 1·15)	0·29	..	..
Components of the neonatal outcome						
Neonatal death	6/597 (1%)	1/600 (<1%)	0·17 (0·06 to 0·49)	0·0009¶	..	..
Bronchopulmonary dysplasia‖	18/574 (3%)	17/580 (3%)	0·94 (0·49 to 1·78)	0·84	..	..
Brain injury on ultrasound scan**	34/574 (6%)	18/584 (3%)	0·50 (0·31 to 0·84)	0·008	..	..

Non effetto su prevenzione del parto pretermine e su outcomes neonatali avversi *(anche se la percentuale lesioni cerebrali e morti neonatali è inferiore nel gruppo progesterone)*

Progesterone è sicuro dal punto di vista dell'outcome neurocomportamentale a 2 anni

MANAGEMENT STRATEGIES

CERCHIAGGIO CERVICALE

Intervento chirurgico volto a fornire supporto strutturale alla cervice uterina e mantenere l'integrità dello strato mucoso, evitando il suo accorciamento o dilatazione e prevenendo o posticipando il PPT

Shirodkar 1955

Per via transvaginale, dopo mobilizzazione vescicale, per inserimento sopra il livello dei legamenti cardinali

Gibb 1995

Antonhy 1997

Transaddominale (LPT o LPS) con posizionamento della sutura a livello della giunzione cervico-istmica

McDonald 1957

Per via transvaginale, a livello della giunzione cervico.vaginale, senza mobilizzazione della vescica

CERCHIAGGIO CERVICALE

HISTORY-INDICATED

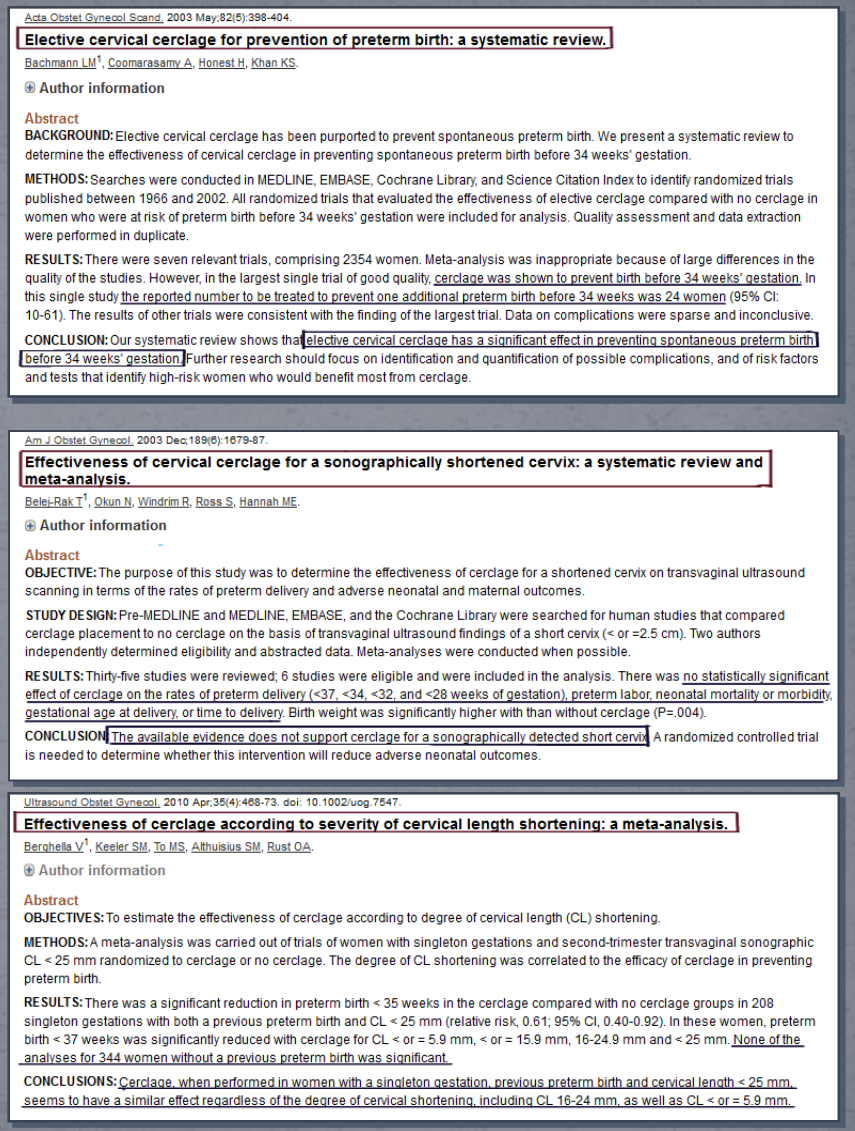
- Profilattico in pazienti asintomatiche
- Posizionato in elezione a 12-14 sg
- RCOG e ACOG: dopo 3 o più PPT e/o aborti tardivi
- Si ottiene piccola riduzione del tasso di PPT (prevenzione di 1 PPT ogni 24 donne trattate)

ULTRASOUND-INDICATED

- Terapeutico con cervicometria < 25 mm a 14-24 sg o in pazienti con FR per PPT e rapido raccorciamento della cervice
- Non sembra portare beneficio in pz con incidentale riscontro di cervicometria ridotta senza storia di PPT o aborto tardivo
- Permette riduzione del tasso di PPT in gravide con storia di PPT o aborto tardivo e cervicometria ridotta

CERCHIAGGIO RESCUE

- Intervento estremo in caso di dilatazione cervicale e/o protrusione delle membrane in vagina



Acta Obstet Gynecol Scand. 2003 May;82(5):398-404.

Elective cervical cerclage for prevention of preterm birth: a systematic review.

Bachmann LM[1], Coomarasamy A, Honest H, Khan KS.

Author information

Abstract

BACKGROUND: Elective cervical cerclage has been purported to prevent spontaneous preterm birth. We present a systematic review to determine the effectiveness of cervical cerclage in preventing spontaneous preterm birth before 34 weeks' gestation.

METHODS: Searches were conducted in MEDLINE, EMBASE, Cochrane Library, and Science Citation Index to identify randomized trials published between 1966 and 2002. All randomized trials that evaluated the effectiveness of elective cerclage compared with no cerclage in women who were at risk of preterm birth before 34 weeks' gestation were included for analysis. Quality assessment and data extraction were performed in duplicate.

RESULTS: There were seven relevant trials, comprising 2354 women. Meta-analysis was inappropriate because of large differences in the quality of the studies. However, in the largest single trial of good quality, cerclage was shown to prevent birth before 34 weeks' gestation. In this single study the reported number to be treated to prevent one additional preterm birth before 34 weeks was 24 women (95% CI: 10-61). The results of other trials were consistent with the finding of the largest trial. Data on complications were sparse and inconclusive.

CONCLUSION: Our systematic review shows that elective cervical cerclage has a significant effect in preventing spontaneous preterm birth before 34 weeks' gestation. Further research should focus on identification and quantification of possible complications, and of risk factors and tests that identify high-risk women who would benefit most from cerclage.

Am J Obstet Gynecol. 2003 Dec;189(6):1679-87.

Effectiveness of cervical cerclage for a sonographically shortened cervix: a systematic review and meta-analysis.

Belej-Rak T[1], Okun N, Windrim R, Ross S, Hannah ME.

Author information

Abstract

OBJECTIVE: The purpose of this study was to determine the effectiveness of cerclage for a shortened cervix on transvaginal ultrasound scanning in terms of the rates of preterm delivery and adverse neonatal and maternal outcomes.

STUDY DESIGN: Pre-MEDLINE and MEDLINE, EMBASE, and the Cochrane Library were searched for human studies that compared cerclage placement to no cerclage on the basis of transvaginal ultrasound findings of a short cervix (< or =2.5 cm). Two authors independently determined eligibility and abstracted data. Meta-analyses were conducted when possible.

RESULTS: Thirty-five studies were reviewed; 6 studies were eligible and were included in the analysis. There was no statistically significant effect of cerclage on the rates of preterm delivery (<37, <34, <32, and <28 weeks of gestation), preterm labor, neonatal mortality or morbidity, gestational age at delivery, or time to delivery. Birth weight was significantly higher with than without cerclage (P=.004).

CONCLUSION: The available evidence does not support cerclage for a sonographically detected short cervix. A randomized controlled trial is needed to determine whether this intervention will reduce adverse neonatal outcomes.

Ultrasound Obstet Gynecol. 2010 Apr;35(4):468-73. doi: 10.1002/uog.7547.

Effectiveness of cerclage according to severity of cervical length shortening: a meta-analysis.

Berghella V[1], Keeler SM, To MS, Althuisius SM, Rust OA.

Author information

Abstract

OBJECTIVES: To estimate the effectiveness of cerclage according to degree of cervical length (CL) shortening.

METHODS: A meta-analysis was carried out of trials of women with singleton gestations and second-trimester transvaginal sonographic CL < 25 mm randomized to cerclage or no cerclage. The degree of CL shortening was correlated to the efficacy of cerclage in preventing preterm birth.

RESULTS: There was a significant reduction in preterm birth < 35 weeks in the cerclage compared with no cerclage groups in 208 singleton gestations with both a previous preterm birth and CL < 25 mm (relative risk, 0.61; 95% CI, 0.40-0.92). In these women, preterm birth < 37 weeks was significantly reduced with cerclage for CL < or = 5.9 mm, < or = 15.9 mm, 16-24.9 mm and < 25 mm. None of the analyses for 344 women without a previous preterm birth was significant.

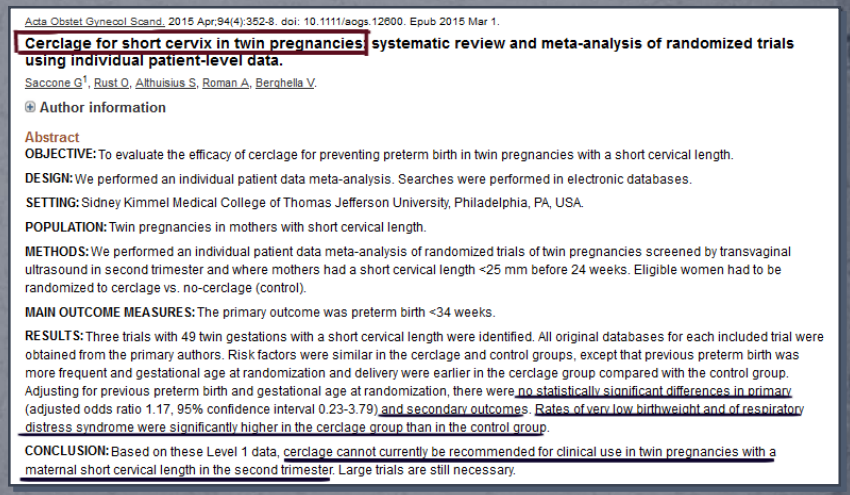
CONCLUSIONS: Cerclage, when performed in women with a singleton gestation, previous preterm birth and cervical length < 25 mm, seems to have a similar effect regardless of the degree of cervical shortening, including CL 16-24 mm, as well as CL < or = 5.9 mm.

CERCHIAGGIO CERVICALE

Contraindication	Complication[2]
• Fetal anomaly incompatible with life • Intrauterine infection • Active bleeding • Active preterm labour • Ruptured membranes • Fetal demise	• Serious complication 1 in 50 • Anaesthetic • Postop abdominal pain, bleeding, bladder injury • Ruptured membranes (2% elective, up to 65% non-elective) • Chorioamnionitis 1-8% • Preterm labour • Fetal loss • Cervical laceration • Cervical dystocia • Difficulty removing suture 1%

- ✓ Tecnica invasiva che richiede anestesia
- ✓ Non scevra di complicanze
- ✓ Non sempre efficace nella prevenzione del PPT

- ✓ NON ruolo significativo del cerchiaggio nelle gravidanze gemellari in cui è dimostrato :
  - assenza di differenza statisticamente significativa negli outcomes primari e secondari
  - aumento di VLBW e sindrome da distress respiratorio nella pazienti cerchiate



Acta Obstet Gynecol Scand. 2015 Apr;94(4):352-8. doi: 10.1111/aogs.12600. Epub 2015 Mar 1.

Cerclage for short cervix in twin pregnancies: systematic review and meta-analysis of randomized trials using individual patient-level data.

Saccone G[1], Rust O, Althuisius S, Roman A, Berghella V.

Author information

Abstract

OBJECTIVE: To evaluate the efficacy of cerclage for preventing preterm birth in twin pregnancies with a short cervical length.

DESIGN: We performed an individual patient data meta-analysis. Searches were performed in electronic databases.

SETTING: Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA.

POPULATION: Twin pregnancies in mothers with short cervical length.

METHODS: We performed an individual patient data meta-analysis of randomized trials of twin pregnancies screened by transvaginal ultrasound in second trimester and where mothers had a short cervical length <25 mm before 24 weeks. Eligible women had to be randomized to cerclage vs. no-cerclage (control).

MAIN OUTCOME MEASURES: The primary outcome was preterm birth <34 weeks.

RESULTS: Three trials with 49 twin gestations with a short cervical length were identified. All original databases for each included trial were obtained from the primary authors. Risk factors were similar in the cerclage and control groups, except that previous preterm birth was more frequent and gestational age at randomization and delivery were earlier in the cerclage group compared with the control group. Adjusting for previous preterm birth and gestational age at randomization, there were no statistically significant differences in primary (adjusted odds ratio 1.17, 95% confidence interval 0.23-3.79) and secondary outcomes. Rates of very low birthweight and of respiratory distress syndrome were significantly higher in the cerclage group than in the control group.

CONCLUSION: Based on these Level 1 data, cerclage cannot currently be recommended for clinical use in twin pregnancies with a maternal short cervical length in the second trimester. Large trials are still necessary.

Abbott et al 2012; Lo et al 2009; Abdel-Aleem et al 2013

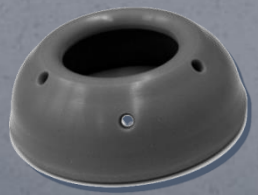
SVILUPPO DEL CONCETTO DI PESSARIO PER LA PREVENZIONE DEL PPT

A partire dagli anni '50 venivano utilizzati per la prevenzione del PPT pessari ideati per il prolasso genitale

- ✓ Cross 1959: Ring pessary in 13 pazienti con storia di lacerazioni cervicali, incompetenza cervicale, utero didelfo
- ✓ Vitsky 1963: Hodge pessary in 21 pazienti
- ✓ Oster e Javert 1966: Hodge pessary in 29 pazienti con incompetenza cervicale

L'introduzione di pessari creati specificatamente per le donne in gravidanza si ebbe nei Paesi dell'Est Europa

- ✓ Jorde e Hamann 1978: crearono un pessario butterfly-shaped in plastica o silicone
- ✓ Arabin 1970: introdusse un pessario in silicone malleabile cone-shaped
  Certificazione Europea



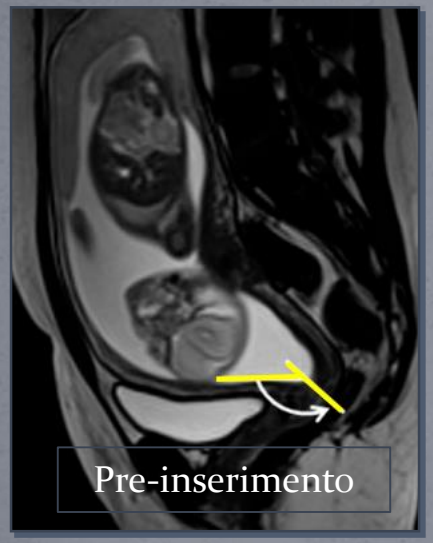
Arabin et al 2013

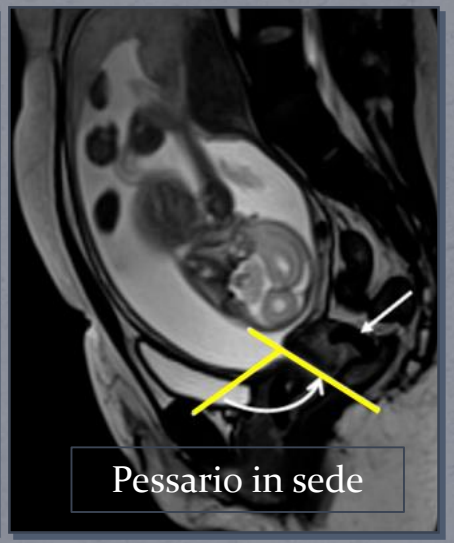
MECCANISMO D'AZIONE

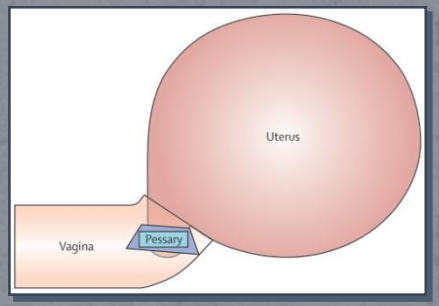
Si ipotizza:

- ❑ Modifica dell'inclinazione della cervice rispetto all'utero rendendola più retroposta e ottenendo un angolo utero-cervicale più acuto:
- ✓ evita la pressione diretta sulle membrane a livello dell'OUI e della cervice stessa
- ✓ direziona più anteriormente il peso dell'utero
- ✓ Previene ulteriori dilatazioni dell'OUI, associate spesso a scollamento delle membrane

Cannie et al 2013; Arabin et al 2013


Pre-inserimento


Pessario in sede




Lunghezza cervice

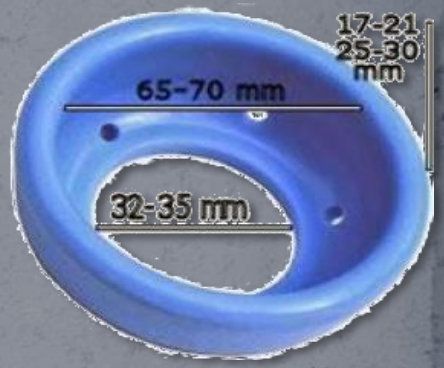
- ❑ Mantenimento del tappo di muco cervicale, che sembra svolgere un importante ruolo di protezione della cavità uterina da infezioni ascendenti
- ❑ Favorisce ispessimento e edemizzazione del collo

Becher et al 2009; Lee DC et al 2011

TECHNICAL CONSIDERATIONS

✓ DIMENSIONI

Clinical situation & results from TVS	Proximal inner diameter 32 mm	Proximal inner diameter 35 mm	Distal outer diameter 65 mm	Distal outer diameter 70 mm	Height 17 mm	Height 21 mm	Height 25 mm	Height 30 mm
Short cervix 2nd trimester								
Singleton								
No or Y-shaped funneling								
Nulliparous	√		√			√		
Parous	√			√		√		
V- or U-shaped funneling								
Nulliparous		√	√			√		
Parous		√		√		√		
Twins								
No funneling								
Nulliparous	√		√				√	
Parous	√			√			√	
V- or U-shaped funneling								
Nulliparous		√	√				√	
Parous		√		√			√	
Short cervix (e.g. after cone biopsy) 1st trimester								
Singleton								
Nulliparous	√		√		√			
Parous	√			√	√			
Twins								
Nulliparous	√		√			√		
Parous	√			√		√		
Additional signs of 'prolapse' in any patient								
Nulliparous		√	√					√
Parous		√		√				√

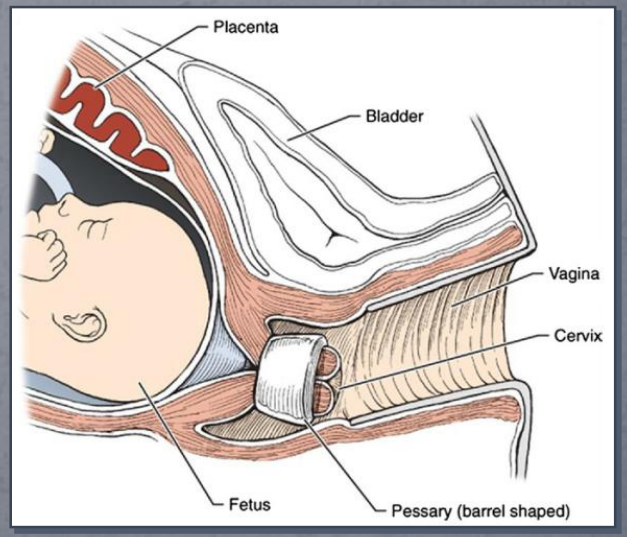


Arabin et al 2013

TECHNICAL CONSIDERATIONS

✓ MODALITA' DI INSERIMENTO

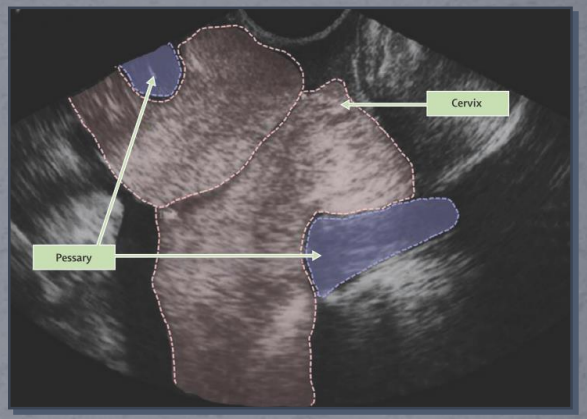
- Esecuzione di cervicometria con valutazione di eventuale funneling
- Esecuzione di tampone vagino-cervicale:
  - Se positività, trattamento farmacologico e dilazionare di 1 settimana il posizionamento
- Non necessaria analgesia/anestesia
- Previa lubrificazione, inserire il pessario in modo che la porzione col diametro minore circondi la cervice e quella con diametro maggiore sia orientata verso il sacro

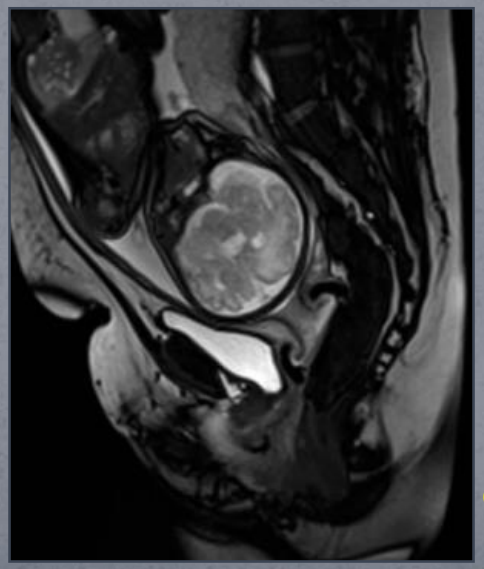


TECHNICAL CONSIDERATIONS

✓ MODALITA' DI INSERIMENTO

- Conferma ecografica di corretto posizionamento

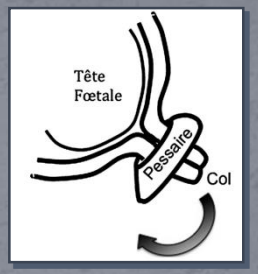




Cannie et al 2013;

TECHNICAL CONSIDERATIONS

✓ MANAGEMENT



- Rimozione di routine a 37 s.g.
- Rimozione prima delle 37 s.g. se:
  - Travaglio di parto
  - Taglio cesareo

  In presenza di attività contrattile, il mantenimento in sede del pessario può causare aumento di pressione a livello cervicale col rischio di lesioni o congestione venosa
  - p-PROM

  E' possibile lasciare il pessario in sede se assenza di contrazione e esclusione di corionamniotite
  - Sanguinamento vaginale
- Non necessario ricovero

  Tranne se cervicometria ridotta precocemente, o presenza di sludge, funneling severo, scollamento, dilatazione
- Controindicazioni al posizionamento
  - *Morte fetale*
  - *Sospetto di corionamnionite*
  - *Sacco in vagina*
  - *PROM*
  - *Sanguinamento vaginale attivo*
  - *Dolore*
  - *Contrazioni o travaglio in atto*

TECHNICAL CONSIDERATIONS

✓ MANAGEMENT

- Buona tolleranza

Dai questionari di valutazione somministrati, il 75% delle pazienti sarebbe disposto a utilizzarlo anche nella successiva gravidanza

- Possibile somministrare antibiotici o progesterone vaginale

In caso di sviluppo di infezione vaginale in corso di gravidanza, è indicato suo trattamento e NON è raccomandata la rimozione del pessario

- Assenza di effetti collaterali materni o fetali

- Assenza di differenze in termini di dati microbiologici e morbidità puerperale in donne che hanno fatto uso di pessario rispetto ai controlli

IN LETTERATURA..

RISULTATI PRIMA DEL 2000

- ✓ Von Foster et al, 1986: primo studio randomizzato di confronto tra uso del cerchiaggio (112 donne) versus pessario (130 donne) → NON differenza statisticamente significativa tra i due gruppi

! Byas in randomizzazione, criteri di inclusione e esclusione, popolazione eterogenea!

- ✓ Newcomer J et al, 2000: prima revisione della letteratura sull'utilizzo del pessario:
  - 8 studi retrospettivi
  - 2 studi prospettici
  - 1 studio randomizzato

→

- Il pessario risulta un'opzione promettente che prolunga l'epoca gestazionale
- Suo utilizzo assieme al cerchiaggio o per donne non eleggibili al cerchiaggio
- Possibile utilizzo in pz a rischio per cervicometria ridotta

IN LETTERATURA..

NEGLI ANNI 2000

- ✓ Arabin et al, 2003: studio retrospettivo di confronto tra gruppo pessario e gruppo expectant management
  - 24 gravidanze singole a rischio per PPT
  - 46 gemellari
    con cervicometria < 15 mm a 22-24 sg

  → Riduzione statisticamente significativa del rischio di PPT con l'uso del pessario (sia nelle gravidanze singole che gemellari)

- ✓ Acharya et al, 2006: studio prospettico di 29 pz a rischio per PPT e con cervicometria < 25 mm prima delle 30 sg

  → Tasso di PPT < 34 sg del 45%
  Assenza di gruppo di controllo

- ✓ Sieroszewski et al, 2009: studio su 54 pz con cervicometria 15-30 mm prima delle 28 sg

  → Tasso di PPT del 16,7%
  Assenza di gruppo di controllo

- ✓ Kimber-Trojnar et al, 2010: studio su 56 pz divise in 2 gruppi (cervicometria ridotta versus pz a rischio per PPT)

  → Tasso di PPT del 14,3%, non differenza tra i gruppi

IN LETTERATURA..

COCHRANE DATABASE 2010

Non sono presenti in letteratura studi metodologicamente soddisfacenti per la valutazione dell'efficacia del pessario nella riduzione del PPT, ma gli studi fino ad ora condotti sembrano suggerire un beneficio apportato dal pessario

GLI STUDI RANDOMIZZATI

Lancet. 2012 May 12;379(9828):1800-6. doi: 10.1016/S0140-6736(12)60030-0. Epub 2012 Apr 3.

Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial.

Goya M[1], Pratcorona L, Merced C, Rodó C, Valle L, Romero A, Juan M, Rodríguez A, Muñoz B, Santacruz B, Bello-Muñoz JC, Llurba E, Higueras T, Cabero L, Carreras E; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group.

Am J Perinatol. 2013 Apr;30(4):283-8. doi: 10.1055/s-0032-1322550. Epub 2012 Aug 8.

Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial.

Hui SY[1], Chor CM, Lau TK, Lao TT, Leung TY.

Lancet. 2013 Oct 19;382(9901):1341-9. doi: 10.1016/S0140-6736(13)61408-7. Epub 2013 Aug 5.

Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial.

Liem S[1], Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, Brons J, Duvekot H, Bijvank BN, Franssen M, Gaugler I, de Graaf I, Oudijk M, Papatsonis D, Pernet P, Porath M, Scheepers L, Sikkema M, Sporken J, Visser H, van Wijngaarden W, Woiski M, van Pampus M, Mol BW, Bekedam D.

N Engl J Med. 2016 Mar 17;374(11):1044-52. doi: 10.1056/NEJMoa1511014.

A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth.

Nicolaides KH[1], Syngelaki A[1], Poon LC[1], Picciarelli G[1], Tul N[1], Zamprakou A[1], Skyfta E[1], Parra-Cordero M[1], Palma-Dias R[1], Rodriguez Calvo J[1].

Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial

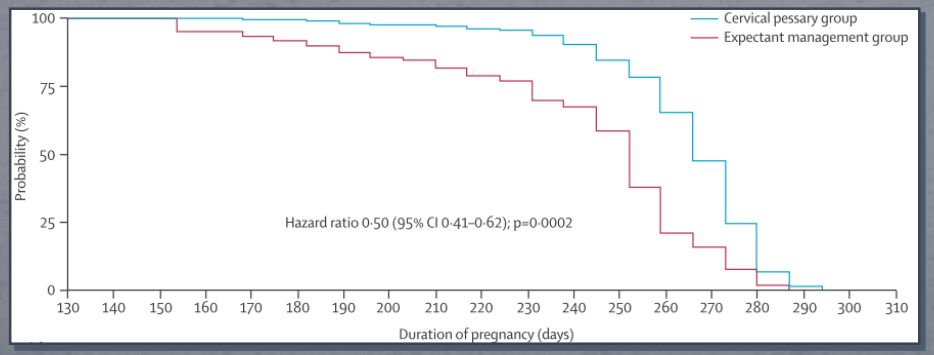
Maria Goya, Laia Pratcorona, Carme Merced, Carlota Rodó, Leonor Valle, Azahar Romero, Miquel Juan, Alberto Rodríguez, Begoña Muñoz, Belén Santacruz, Juan Carlos Bello-Muñoz, Elisa Llurba, Teresa Higueras, Luis Cabero, Elena Carreras*, on behalf of the Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group*

BACKGROUND: Most previous studies of the use of cervical pessaries were either retrospective or case controlled and their results showed that this intervention might be a preventive strategy for women at risk of preterm birth; no randomised controlled trials have been undertaken. We therefore undertook a randomised, controlled trial to investigate whether the insertion of a cervical pessary in women with a short cervix identified by use of routine transvaginal scanning at 20-23 weeks of gestation reduces the rate of early preterm delivery.

METHODS: The Pesario Cervical para Evitar Prematuridad (PECEP) trial was undertaken in five hospitals in Spain. Pregnant women (aged 18-43 years) with a cervical length of 25 mm or less were randomly assigned according to a computer-generated allocation sequence by use of central telephone in a 1:1 ratio to the cervical pessary or expectant management (without a cervical pessary) group. Because of the nature of the intervention, this study was not masked. The primary outcome was spontaneous delivery before 34 weeks of gestation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00706264.

FINDINGS: 385 pregnant women with a short cervix were assigned to the pessary (n=192) and expectant management groups (n=193), and 190 were analysed in each group. Spontaneous delivery before 34 weeks of gestation was significantly less frequent in the pessary group than in the expectant management group (12 [6%] vs 51 [27%], odds ratio 0·18, 95% CI 0·08-0·37; p<0·0001). No serious adverse effects associated with the use of a cervical pessary were reported.

INTERPRETATION: Cervical pessary use could prevent preterm birth in a population of appropriately selected at-risk women previously screened for cervical length assessment at the midtrimester scan.



Nel gruppo pessario riscontro di minor tasso di PPT:

< 28 sg 2% vs 8%
< 34 sg 6% vs 27%
< 37 sg 22% vs 59%

con differenza statisticamente significativa nell'outcome neonatale

Il pessario cervicale permette di prevenire il PPT nelle pz con cervicometria ridotta nel II trimestre

Cerclage Pessary for Preventing Preterm Birth in Women with a Singleton Pregnancy and a Short Cervix at 20 to 24 Weeks: A Randomized Controlled Trial

Shuk Yi Annie Hui, M.R.C.O.G.[1] Chung Ming Chor, M.R.C.O.G.[1] Tze Kin Lau, M.D., F.R.C.O.G.[2]
Terence T. Lao, M.D., F.R.C.O.G.[1] Tak Yeung Leung, M.D., F.R.C.O.G.[1]

OBJECTIVE: To determine the effectiveness of cerclage pessary in the prevention of preterm birth in asymptomatic Chinese women with a short cervix at 20 to 24 weeks.

METHODS: Low-risk women carrying singleton pregnancies were screened with transvaginal ultrasound, and those with a cervical length <25 mm at 20 to 24 weeks were recruited into a randomized controlled trial, comparing the prophylactic use of cerclage pessary with expectant management. The analysis was by intent-to-treat. The primary outcome measure was preterm delivery before 34 weeks.

RESULTS: Among 4438 screened women, 203 women (4.6%) met the inclusion criteria and 108 (58%) consented for the study. A total of 53 and 55 women were allocated to pessary and control groups, respectively. There was no difference in background demographics, including the mean cervical length (19.6 mm versus 20.5 mm) and the mean gestational age at randomization (both 21.9 weeks). Delivery before 34 weeks occurred in 9.4% and 5.5% (p = 0.46) in the pessary and the control groups, respectively. No differences in major side effects were noted between the groups.

CONCLUSION: In our population, <5% had a cervical length of less than 25 mm at 20 to 24 weeks' gestation. The prophylactic use of cerclage pessary did not reduce the rate of preterm delivery before 34 weeks.

No differenza statisticamente significativa nel tasso di parti < 28, 34 o 37 sg

Mean gestational age at delivery

- 38 sg in gruppo pessario
- 37,8 sg in gruppo controllo

Popolazione a più basso rischio?
Diversa metodologia?

L'uso del pessario in pz con cervicometria ridotta non è utile nel ridurre il tasso di PPT

Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial

Sophie Liem, Ewoud Schuit, Maud Hegeman, Joke Bais, Karin de Boer, Kitty Bloemenkamp, Jozien Brons, Hans Duvekot, Bas Nij Bijvank, Maureen Franssen, Ingrid Gaugler, Irene de Graaf, Martijn Oudijk, Dimitri Papatsonis, Paula Pernet, Martina Porath, Liesbeth Scheepers, Marko Sikkema, Jan Sporken, Harry Visser, Wim van Wijngaarden, Mallory Woiski, Mariëlle van Pampus, Ben Willem Mol, Dick Bekedam

Abstract

BACKGROUND: In women with a multiple pregnancy, spontaneous preterm delivery is the leading cause of perinatal morbidity and mortality. Interventions to reduce preterm birth in these women have not been successful. We assessed whether a cervical pessary could effectively prevent poor perinatal outcomes.

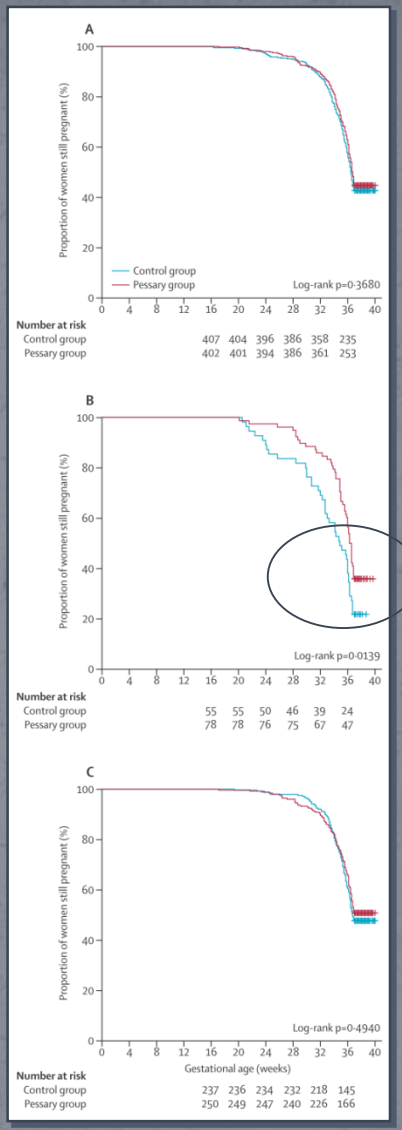
METHODS: We undertook a multicentre, open-label randomised controlled trial in 40 hospitals in the Netherlands. We randomly assigned women with a multiple pregnancy between 12 and 20 weeks' gestation (1:1) to pessary or control groups, using a web-based application with a computer-generated list with random block sizes of two to four, stratified by hospital. Participants and investigators were aware of group allocation. For women in the pessary group, a midwife or obstetrician inserted a cervical pessary between 16 and 20 weeks' gestation. Women in the control group did not receive the pessary, but otherwise received similar obstetrical care to those in the pessary group. The primary outcome was a composite of poor perinatal outcome: stillbirth, periventricular leucomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis, and neonatal death. Analyses were by modified intention to treat. This trial is registered in the Dutch trial registry, number NTR1858.

FINDINGS: Between Sept 21, 2009, and March 9, 2012, 813 women underwent randomisation, of whom 808 were analysed (401 in the pessary group; 407 in the control group). At least one child of 53 women (13%) in the pessary group had poor perinatal outcome, compared with 55 (14%) in the control group (relative risk 0·98, 95% CI 0·69-1·39).

INTERPRETATION: In unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.

Pessario NON utile nel prevenire PTT e/o outcome neonatali sfavorevoli in pz gemellari non selezionate

In pz gemellari e cervicometria < 25^centile, con pessario riduzione statisticamente significativa dei very preterm delivery (< 28 e 32 sg) e outcome neonatali sfavorevoli



Tutte le donne

cervicometria < 38 mm

Cervicometria > 38 mm

A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth

Kypros H. Nicolaides, M.D., Argyro Syngelaki, Ph.D., Liona C. Poon, M.D., Gemma Picciarelli, M.D., Natasa Tul, M.D., Aikaterini Zamprakou, M.D., Evdoxia Skyfta, M.D., Mauro Parra-Cordero, M.D., Ricardo Palma-Dias, M.D., Ph.D., and Jesus Rodriguez Calvo, M.D.

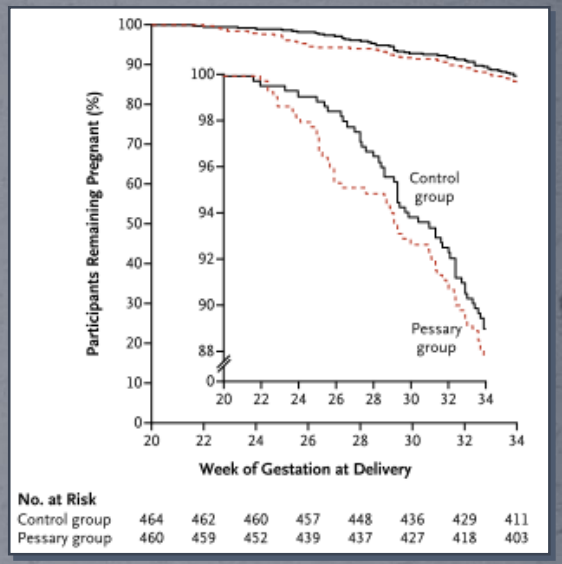
Abstract

BACKGROUND: Preterm birth is the leading cause of neonatal and infant death and of disability among survivors. It is unclear whether a pessary inserted around the cervix reduces the risk of preterm singleton birth.

METHODS: We conducted a multicenter, randomized, controlled trial comparing pessary placement with expectant management (control) in girls and women who were pregnant with singletons (singleton pregnancies) and who had a cervical length of 25 mm or less at 20 weeks 0 days to 24 weeks 6 days of gestation. Participants in either group who had a cervical length of 15 mm or less, at randomization or at subsequent visits, received treatment with vaginal progesterone. The primary outcome was spontaneous delivery before 34 weeks of gestation.

RESULTS: In an intention-to-treat analysis, there was no significant difference between the pessary group (465 participants) and the control group (467 participants) in the rate of spontaneous delivery before 34 weeks (12.0% and 10.8%, respectively; odds ratio in the pessary group, 1.12; 95% confidence interval, 0.75 to 1.69; P=0.57). There were no significant differences in the rates of perinatal death (3.2% in the pessary group and 2.4% in the control group, P=0.42), adverse neonatal outcome (6.7% and 5.7%, respectively; P=0.55), or neonatal special care (11.6% and 12.9%, respectively; P=0.59). The incidence of new or increased vaginal discharge was significantly higher in the pessary group than in the control group.

CONCLUSIONS: Among girls and women with singleton pregnancies who had a short cervix, a cervical pessary did not result in a lower rate of spontaneous early preterm delivery than the rate with expectant management. (Funded by the Fetal Medicine Foundation; Current Controlled Trials number, ISRCTN01096902.).



Nelle pazienti con cervicometria ridotta (< 25 mm) riscontrata nel II trimestre il pessario:

- NON riduce il tasso di PTT
- NON influenza i tassi di morte perinatale e outcome neonatale avverso

PROGESTERONE vs CERCHIAGGIO vs PESSARIO IN GRAVIDANZE SINGOLE

Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix

Z. ALFIREVIC*, J. OWEN†, E. CARRERAS MORATONAS‡, A. N. SHARP*, J. M. SZYCHOWSKI§ and M. GOYA‡

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OBJECTIVE: To compare the outcome of pregnancy in cohorts of women with singleton pregnancy and history of preterm birth and sonographic short cervix managed with different treatment protocols, namely cerclage, vaginal progesterone or cervical pessary.

METHODS: This was a comparison of three management protocols for women with singleton pregnancy and a high risk of preterm birth because of a prior spontaneous preterm birth before 34 weeks and a shortened cervical length detected by transvaginal ultrasound. The study included 142 women who were initially treated with cerclage (USA), 59 with vaginal progesterone (UK) and 42 with cervical pessary (Spain). Perinatal outcomes were compared between the three cohorts.

RESULTS: There were no statistically significant differences in perinatal losses, neonatal morbidity and preterm births among the three groups, apart from a higher rate of preterm birth before 34 weeks' gestation after treatment with vaginal progesterone in comparison with treatment with cervical pessary (32% vs 12%; relative risk (RR) = 2.70; 95% CI, 1.10-6.67). When only the subgroups of women with cervical length < 25 mm, irrespective of gestational age, were compared, the difference between these two cohorts was not statistically significant (RR = 2.21; 95% CI, 0.83-5.89).

CONCLUSION: Cerclage, vaginal progesterone and pessary appear to have similar effectiveness as management strategies in women with singleton pregnancy, previous spontaneous preterm birth and short cervix. Direct randomized comparisons of these strategies, or combinations thereof, are needed to determine optimal management.

Studio retrospettivo di 3 coorti, Ultrasound Obstet Gynecol 2013

Non vi sono differenze statisticamente significative tra le 3 opzioni di trattamento

Table 3 Subgroup analysis including only women who had cervical length < 25 mm, irrespective of gestational age

	Primary therapy for short cervix			*Relative risk (95% CI)*		
Clinical outcome	*Cerclage (A) (n = 142)*	*Vaginal progesterone (B) (n = 38)**	*Cervical pessary (C) (n = 42)*	*A* vs *B*	*A* vs *C*	*B* vs *C*
Birth < 34 weeks	40 (28)	10 (26)	5 (12)	1.07 (0.59–1.94)	2.37 (0.99–5.61)	2.21 (0.83–5.89)
Perinatal loss	12 (8.5)	5 (13)	1 (2)	0.64 (0.24–1.71)	3.55 (0.47–26.51)	5.53 (0.68–45.21)

QUALE FUTURO?

Il pessario è dotato di vantaggi quali:

- Procedura non invasiva
- Operatore indipendente
- Facile da posizionare e da rimuovere
- Poco costoso

GRAVIDANZE SINGOLE A RISCHIO DI PPT

- ✓ In letteratura non c'è attualmente consensus riguardo l'utilizzo del pessario o sua integrazione con altre metodiche nella prevenzione del parto pretermine nelle gravidanze singole a rischio di PPT sia per pregressa storia di parto pretermine che per cervicometria ridotta

QUALE FUTURO?

PREGRESSA CONIZZAZIONE

Il rischio di PTT in questa popolazione rispetto ai controlli è 5 volte superiore dopo 1 conizzazione e 10 volte superiore dopo 2 conizzazioni.

Fino ad oggi, sia il cerchiaggio elettivo che d'emergenza si sono rivelati poco utili nel ridurre il tasso di PTT in questa popolazione

Nam et al, 2010; Ortoft et al, 2010

E' stato condotto uno studio osservazionale su 12 donne con storia di una o più conizzazioni e riscontro di cervicometria media di 19 mm a cui è stato posizionato pessario cervicale a 17 sg:

- Mean gestational age at delivery: 38 sg
- Intervallo medio tra inserzione e parto: 145 giorni

Kyvernitakis et al, 2012

QUALE FUTURO?

GRAVIDANZA GEMELLARE

- ✓ Le donne con gravidanza gemellare hanno un aumentato rischio di parto pretermine spontaneo
- ✓ La cervicometria transvaginale ha un alta sensibilità e specificità nella predizione del parto pretermine in quasi tutte le popolazioni studiate (gravidanze singole, gemellari, asintomatiche, sintomatiche, PPROM)
- ✓ Le gravidanze gemellari asintomatiche con cervice corta hanno un aumentato rischio di parto pretermine spontaneo e ad oggi non esiste alcuna terapia per questa popolazione
- ✓ Tutte le terapie studiate non hanno dimostrato efficacia negli studi randomizzati (progesterone, cerchiaggio, riposo a letto, antibiotico terapia, vitamine…)
  - *Il progesterone NON riduce significativamente il rischio di PPT*
  - *Il cerchiaggio NON ha un ruolo significativo nelle gravidanze multiple e il suo utilizzo sembra aumentare il rischio di PPT*

QUALE FUTURO?

GRAVIDANZA GEMELLARE

Prenat Diagn. 2012 Dec;32(12):1181-5. doi: 10.1002/pd.3982. Epub 2012 Oct 11.

Arabin cervical pessary to prevent preterm birth in severe twin-to-twin transfusion syndrome treated by laser surgery.

Carreras E[1], Arévalo S, Bello-Muñoz JC, Goya M, Rodó C, Sanchez-Duran MA, Peiro JL, Cabero L.

Am J Obstet Gynecol. 2016 Feb;214(2):145-52. doi: 10.1016/j.ajog.2015.11.012. Epub 2015 Nov 25.

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

Goya M[1], de la Calle M[2], Pratcorona L[3], Merced C[3], Rodó C[3], Muñoz B[4], Juan M[5], Serrano A[6], Llurba E[3], Higueras T[3], Carreras E[3], Cabero L[3], PECEP-Twins Trial Group.

J Obstet Gynaecol. 2016 Mar 25:1-4. [Epub ahead of print]

Arabin cervical pessary to prevent preterm birth in twin pregnancies with short cervix.

Di Tommaso M[1], Seravalli V[1], Arduino S[2], Bossotti C[2], Sisti G[1], Todros T[2].

L'uso del pessario nelle gravidanze multiple con cervicometria < 25 mm è associato con la riduzione in PPT

Il pessario nelle gravidanze multiple asintomatiche non selezionate NON influenza il tasso di PPT

Eur J Obstet Gynecol Reprod Biol. 2016 Feb;197:72-7. doi: 10.1016/j.ejogrb.2015.11.001. Epub 2015 Nov 30.

Pessary placement in the prevention of preterm birth in multiple pregnancies: a propensity score analysis.

Monfrance MJ[1], Schuit E[2], Groenwold RH[3], Oudijk MA[4], de Graaf IM[5], Bax CJ[6], Bekedam DJ[7], Mol BW[8], Langenveld J[9].

Am J Obstet Gynecol. 2016 Jan;214(1):3.e1-9. doi: 10.1016/j.ajog.2015.08.051. Epub 2015 Aug 28.

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

Nicolaides KH[1], Syngelaki A[2], Poon LC[2], de Paco Matallana C[3], Plasencia W[4], Molina FS[5], Picciarelli G[6], Tul N[7], Celik E[2], Lau TK[8], Conturso R[9].

Does Cervical Pessary Prevent Spontaneous Preterm Birth in Twin Pregnancies With Short Cervical Length?

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2016 by Federico II University

Sponsor:
Federico II University

Information provided by (Responsible Party):
Gabriele Saccone, Federico II University

ClinicalTrials.gov Identifier:
NCT02708264

First received: March 6, 2016
Last updated: March 9, 2016
Last verified: March 2016
History of Changes

Studio prospettico randomizzato italiano patrocinato SIEOG

BIBLIOGRAFIA_1

1. Abbott D et al Cervical cerclage: a review of current evidence. Aust N Z J Obstet Gynaecol. 2012 Jun;52(3):220-3. doi: 10.1111/j.1479-828X.2012.01412.x. Epub 2012 Feb 15. Review.

2. Abdel-Aleem H et al Cervical pessary for preventing preterm birth. Cochrane Database of Systematic Reviews 2010;9:CD007873.pub2

3. Abdel-Aleem H et al Cervical pessary for preventing preterm birth. Cochrane Database Syst Rev. 2013 May 31;(5):CD007873. doi: 10.1002/14651858.CD007873.pub3. Review.

4. Acharya G et al Noninvasive cerclage for the management of cervical incompetence: a prospective study. Arch Gynecol Obstet 2006;273:283-7.

5. Alfirevic Z et al Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2012 Apr 18;(4):CD008991. doi: 10.1002/14651858.CD008991.pub2. Review.

6. Alfirevic Z et al Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. Ultrasound Obstet Gynecol 2013;41:146-51

7.Arabin B et al Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? J Perinat Med. 2003;31(2):122-33.

8. Arabin B et al pessaries for prevention of spontaneous preterm birth: past, present and future. Ultrasound Obstet Gynecol. 2013 Oct;42(4):390-9. doi: 10.1002/uog.12540. Review.

9. Bachmann LM et al Elective cervical cerclage for prevention of preterm birth: a systematic review. Acta Obstet Gynecol Scand. 2003 May;82(5):398-404. Review.

10. Becher N et al The cervical mucus plug: structured review of the literature. Acta Obstet Gynecol Scand 2009; 88: 502–513.

11. Belej-Rak T et al Effectiveness of cervical cerclage for a sonographically shortened cervix: a systematic review and meta-analysis. Am J Obstet Gynecol. 2003 Dec;189(6):1679-87. Review.

12.Berghella V et al Effectiveness of cerclage according to severity of cervical length shortening: a meta-analysis. Ultrasound Obstet Gynecol. 2010 Apr;35(4):468-73.

13.Cannie MM et al Arabin cervical pessary in women at high risk of preterm birth: a magnetic resonance imaging observational follow-up study. Ultrasound Obstet Gynecol 2013; 42: 426–433.

14.Carreras E et al Arabin cervical pessary to prevent preterm birth in severe twin-to-twin transfusion syndrome treated by laser surgery. Prenat Diagn. 2012 Dec;32(12):1181-5. doi: 10.1002/pd.3982. Epub 2012 Oct 11.

15.Di Tommaso M et al Arabin cervical pessary to prevent preterm birth in twin pregnancies with short cervix. J Obstet Gynaecol. 2016 Mar 25:1-4.

16.Dodd JM et al Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev. 2013 Jul 31;(7):CD004947.

BIBLIOGRAFIA_2

17.Falcão V et al Cervical pessary for the prevention of preterm birth: is it of any use? J Perinat Med. 2016 May 12.
18.Goya M et al Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomized controlled Trial . Lancet 2012;12;379:1800-6.
19.Goya M et al PECEP-Twins Trial Group. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol. 2016 Feb;214(2):
20. Hui AS, Lao TT, Ting YH, Leung TY. Cervical pessary in pregnant women with a short cervix. Lancet 2012;380:887;author's reply 887.
21. Laws PJ et al Australia's mothers and babies 2003: perinatal statistics series number 16. Sydney: AIHW National Perinatal Statistics Unit, 2005
22.Lee DC et al Protein profiling underscores immunological functions of uterine cervical mucus plug in human pregnancy. J Proteomics 2011; 74: 817–828.
23.Lewit EM, Baker LS, Corman H, Shiono PH. The direct cost of low birth weight. Future Child. 1995 Spring;5(1):35-56
24.Lumley J. Defining the problem: the epidemiology of preterm birth. BJOG. 2003 Apr;110 Suppl 20:3-7.
25.Liem S et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013 Oct 19;382(9901):1341-9.
26.Lo C. The incompetent cervix. O&G Magazine 2009;11 (2):30–2.
27.Monfrance MJ et al Pessary placement in the prevention of preterm birth in multiple pregnancies: a propensity score analysis. Eur J Obstet Gynecol Reprod Biol. 2016 Feb;197:72-7. doi: 10.1016/j.ejogrb.2015.11.001. Epub 2015 Nov 30.
28.Nam KH et al Pregnancy outcome after cervical conization: risk factors for preterm delivery and the efficacy of prophylactic cerclage. J Gynecol Oncol 2010; 21: 225–229.
29.Newcomer J. Pessaries for the treatment of incompetent cervix and premature delivery. Obstetrical and Gynecological Survey 2000; 55:443-8.
30.Nicolaides KH et al Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gynecol. 2016 Jan;214(1):3.e1-9. doi: 10.1016/j.ajog.2015.08.051. Epub 2015 Aug 28.
31.Nicolaides KH et al A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth. N Engl J Med. 2016 Mar 17;374(11):1044-52.
32. Ngoc NT et al Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries. Bull World Health Organ. 2006 Sep;84(9):699-705.

BIBLIOGRAFIA_3

33.Norman JE et al OPPTIMUM study group. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet. 2016 May 21;387(10033):2106-16.

34.Ortoft G et al After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy. BJOG 2010; 117: 258–267

35.Rafael et al Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. Cochrane Database Syst Rev. 2014 Sep 10;(9):CD009166. doi: 10.1002/14651858.CD009166.pub2. Review.

36.Saccone G et al Cerclage for short cervix in twin pregnancies: systematic review and meta-analysis of randomized trials using individual patient-level data. Acta Obstet Gynecol Scand. 2015 Apr;94(4):352-8. doi: 10.1111/aogs.12600. Epub 2015 Mar 1. Review.

37.Shennan AH. Guidelines Comminttee of the Royal College of Obstetricians and Gynaecologists. Cervical cerclage. RCOG Green-top Guideline No. 60 May 2011

38.Sieroszewski P et al The Arabin pessary for the treatment of threatened mid-trimester miscarriage or premature labour and miscar - riage: a case series. J Matern Fetal Neonatal Med 2009;22:469-472.

39.Kimber-Trojnar Z et al Pessary use for the treatment of cervical incompetence and prevention of preterm labour. J Matern Fetal Neonatal Med 2010;23:1493-1499.

40.Kyvernitakis I et al Is Early Treatment with a Cervical Pessary an Option in Patients with a History of Surgical Conisation and a Short Cervix? Geburtshilfe Frauenheilkd. 2014 Nov;74(11):1003-1008.

41.Von Forster F et al Treatment of cervix incompetence-cerclage versus pessary? Zentralblatt fur Gynakologie 1986;108:230-7.