Is cerclage safe and effective in preventing preterm birth in women presenting early in pregnancy with cervical dilatation?

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Uncertainties

Is cerclage safe and effective in preventing preterm birth in women presenting early in pregnancy with cervical dilatation?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Box Start
What you need to know

- Emergency cervical cerclage is a potential treatment for women presenting with cervical dilatation and exposed unruptured fetal membranes before 28 weeks of pregnancy in the absence of bleeding, uterine activity, or infection
- There is limited low quality evidence mainly from retrospective studies that emergency cervical cerclage may prolong pregnancy duration, but concerns regarding selection bias and reporting of complications restrict their clinical interpretation.
- There is no evidence to support the use of progesterone, NSAIDs, pessary, prophylactic antibiotics, or tocolytics as independent treatments in these women

Box End

Preterm birth is an important cause of maternal and neonatal morbidity and neonatal mortality globally accounting for almost 1 million neonatal deaths each year (Liu et al 2016). Women who present with a dilated cervix in the second trimester with minimal or no preceding symptoms are at increased risk of pregnancy loss and preterm birth (fig 1). Emergency cervical cerclage, or rescue cerclage, is performed to prevent this. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend considering this procedure for women presenting with cervical dilatation and exposed fetal membranes between 16 and 28 weeks of gestation if there are no signs of bleeding, infection, or uterine activity (see box 1).[1]

Fig 1. Premature cervical dilatation and exposed unruptured fetal membranes

Box Start

Box 1. NICE guidelines for management of preterm labour and birth (NG25)[1]

Women with a closed cervix

- For women with a history of spontaneous preterm birth or second trimester miscarriage, *plus* a cervical length of <25 mm on transvaginal ultrasound (TVUSS): offer a choice of prophylactic cervical cerclage or progesterone.
- For women with a history of spontaneous preterm birth or second trimester miscarriage, *or* a cervical length of <25 mm on TVUSS (but not both): consider progesterone.
- For women with a history of preterm premature rupture of the membranes (PPROM) or cervical trauma, *plus* a cervical length of <25 mm on TVUSS: offer prophylactic cervical cerclage.

Women with cervical dilatation and exposed unruptured fetal membranes*

- Do not offer "rescue" cerclage if there are signs of infection, bleeding, or uterine activity.
- Consider rescue cerclage for women between 16+0 and 27+6 weeks of gestation, taking into account gestational age and degree of dilatation, and in discussion with consultant obstetrician and paediatrician.
- Explain to women the risks of the procedure and that the aim is to delay birth to increase the likelihood of survival and decrease neonatal morbidity.

*NICE guidance does not discuss any interventions other than emergency cervical cerclage (rescue cerclage) for women with cervical dilatation and exposed membranes.

Box End

Asymptomatic women with a history of preterm birth or spontaneous miscarriage and a short cervix may be considered for prophylactic cervical cerclage (performed when the cervix

is closed and the membranes are not exposed); this procedure is not the focus of this paper. Likewise, management of women presenting early in gestation with contractions, vaginal bleeding, or ruptured membranes is not part of this article.

Emergency cervical cerclage (ECC) tends to be complex as membranes must be replaced within the uterus and a stitch placed around any remaining cervix. The procedure carries a risk of complications such as membrane rupture, maternal or fetal infection, sepsis, cervical trauma, and worsening clinical scenario.

There is uncertainty about the benefits and risks of ECC and other management options to prevent preterm birth and pregnancy loss in women with dilated cervix and exposed unruptured fetal membranes.

What is the evidence of uncertainty?

There is limited, low quality evidence that ECC prolongs pregnancy duration and reduces pregnancy loss in these women. It is unclear how variable presentations, gestation, infection, and add-on treatments influence outcomes with emergency cervical cerclage and risks for mother and baby.[2 3]

Box start

GRADE quality of evidence and definitions

High quality—Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality—Any estimate of effect is very uncertain

Box end

A systematic review and meta-analysis published in 2020 (12 observational studies, 1021 participants) found that ECC in singleton pregnancies decreased preterm birth (odds ratio 0.25 (95% confidence interval 0.16 to 0.39), 5 studies, n=392) and pregnancy loss (OR 0.26 (0.12 to 0.56), 8 studies, n=455) compared with expectant management.[2] Emergency cervical cerclage was found to increase ~~mean~~ pregnancy duration by 47.45 days (95% CI 39.89 to 55.0). The evidence is of low to very low ~~quality~~.

However, unlike other options, the consequences of ECC may shorten the pregnancy (due to rupture of membranes or infection). The reporting of complication rates in existing literature is very poor. Reported rates of rupture or membranes vary from 5-25% (Olatunbosun et al 1995, Proctor et al 2021). Depending on gestation, this may cause loss of the pregnancy or limit the chance of survival. It is also possible for ECC to prolong

pregnancy without meaningful improvement in the chance of live birth or survival to childhood particularly at earlier gestations of presentation (box 2). Advances in neonatal care mean a significant number of extremely preterm babies (22-27 weeks) will survive to neonatal unit admission but overall, mortality, and significant morbidity, in surviving infants remains very high (Mactier et al 2019).

Box Start

Box 2. Gestation calculator

At 24 weeks, 6 out of every 10 babies are expected to survive; at 28 weeks, 9 out of 10 babies will survive; and at 34 weeks, survival is equivalent to that of full term babies[4 5]

Gestation at presentation	Prolongation required to reach gestation		
	24/40	28/40	34/40
16+0	56 days	84 days	126 days
18+0	42 days	70 days	112 days
20+0	28 days	56 days	98 days
22+0	14 days	42 days	84 days
24+0	0	28 days	70 days
26+0	0	14 days	56 days
28+0	0	0	42 days

Green—The mean pregnancy prolongation* for emergency cervical cerclage (ECC) and bed rest are expected to result in reaching the given gestation

Yellow—The mean pregnancy prolongation* for ECC but not bed rest is expected to result in reaching the given gestation

Red—The mean pregnancy prolongation* for neither ECC or bed rest are expected to result in reaching the given gestation

*The trial by Althusius et al[6] found mean prolongation of pregnancy of 54 days in the ECC arm and 20 days in the bed rest arm.

Box End

A small randomised controlled trial (23 women (16 singleton and 7 twin pregnancies)), found that ECC led to a statistically significant improvement in time to delivery compared with bed rest (54 *v* 20 days, P=0.46) and composite neonatal outcome (risk ratio 1.6 (95% CI 1.1 to 2.3)).[6] It lowered preterm birth before 34 weeks (7/13 in ECC group *v* 10/10 in bed rest group, P=0.2). Both groups received antibiotic prophylaxis. Women in the cerclage group received indomethacin in addition.[6] Results should be interpreted with caution because of fewer twin pregnancies and use of indomethacin in the cerclage group. There was no long term follow-up of mothers or babies. A trial of ECC compared with no cerclage in women with twin pregnancy (30 women) found similar reduction in preterm birth at <34 weeks (risk ratio 0.71 (95% CI 0.52 to 0.96)) and perinatal mortality.[7] All women in the cerclage group received indomethacin and antibiotics.

Progesterone, non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, pessaries, and prophylactic antibiotics have been variably used as adjuncts to ECC in small studies (box 3). There is little evidence to recommend their use as independent treatments for

this condition. Urinary tract infection and bacterial vaginosis may cause cervical dilatation and increase the risk of preterm birth. Antibiotics may be used if infection is suspected or confirmed, but there is no evidence for prophylactic antibiotic use.

Box Start

Box 3. Summary of evidence for interventions in women with cervical dilatation and exposed fetal membranes (in the absence of uterine contractions)

Antibiotics

A Cochrane review of prophylactic antibiotics in women in spontaneous preterm birth with intact membranes found no significant reduction in birth within 48 hours (relative risk 1.02 (95% CI 0.89 to 1.18), 4 trials, n=6800) or preterm birth <36 weeks (RR 0.98 (0.92 to 1.04), 8 trials, n=7185). Antibiotic use was associated with increased risk of harm to neonates.[8] There was an increased risk of neonatal death with any antibiotic compared with placebo (RR 1.57 (1.03 to 2.40), 9 studies, n=7248).

One randomised controlled trial[9] (n=84) in women with painless cervical dilatation and exposed membranes found no significant difference in preterm birth <34 weeks (25.6% in antibiotic group *v* 40% in placebo group, P value not significant, not otherwise specified) or in composite neonatal outcome (2.6% *v* 17.5%, P value not significant). There was also no evidence of benefit of antibiotics in preventing preterm birth or neonatal outcome in the subgroup with confirmed microbial invasion of the amniotic cavity (preterm birth <34 weeks 50% in antibiotic group *v* 100% in placebo group, P value not significant).

One small single centre RCT (n=53) randomised women undergoing emergency cervical cerclage (ECC) to either ECC alone or ECC plus indomethacin and antibiotics.[10] Adjunctive use of indomethacin and antibiotics were associated with a significant increase in the percentage of women with an ongoing pregnancy at 28 days (92.3% (n=24) *v* 62.5% (n=15), P=0.01). There was no difference in gestation at delivery overall or neonatal outcomes.

Arabin pessary

Low quality evidence from one retrospective observational study comparing pessary, ECC, and expectant management in women with an open cervix (n=112) suggests no significant difference in gestation at delivery between pessary and expectant management.[11] ECC was associated with a significant increase in gestational age at delivery (mean 22.9 (SD 4.5) weeks with pessary, 25.6 (6.7) weeks with expectant management, and 29.2 (7.5) weeks with cerclage, P=0.015). There is no RCT or meta-analysis evidence for the use of cervical pessaries in women with an open cervix.

Cervical cerclage

One small RCT at high risk of bias compared ECC with bed rest.[6] ECC was found to increase pregnancy length (mean time from intervention to delivery 54 *v* 20 days, P=0.46) and reduce neonatal morbidity (compound outcome) compared with controls (risk ratio 1.6 (95% CI 1.1 to 2.3)). A 2020 systematic review and meta-analysis of observational data(12 observational studies, 2 at low risk of bias) supports a reduction in preterm birth and prolongation of pregnancy with ECC compared with expectant management, but most of these studies are small, retrospective, and at high risk of bias. ECC was associated with a reduction in risk of preterm birth <28 weeks (odds ratio 0.25 (95% CI 0.16 to 0.39), 5 studies, n=392).

Indomethacin

Indomethacin is an NSAID and potential uterine muscle relaxant sometimes used at the time of ECC. There is no role for indomethacin as a stand-alone treatment for women with cervical dilatation.

One small single centre RCT (n=53) randomised women undergoing ECC to either ECC alone or to ECC plus indomethacin and antibiotics.[10] Adjunctive use of indomethacin and antibiotics were associated with an increase in the percentage of women with an ongoing

pregnancy at 28 days (92.3% (n=24) *v* 62.5% (n=15), P=0.01). There was no significant difference in gestation at delivery overall or neonatal outcomes.

A retrospective observational study (n=222) of women undergoing ECC compared women who received indomethacin (31%) with those who did not and found no significant difference in risk of preterm birth <32 or <35 weeks.[12]

Progesterone

There is no RCT or meta-analysis evidence for the use of progesterone in the prevention of preterm birth or late miscarriage in women with an open cervix and exposed fetal membranes.

A small observational study (n=69) which included women with a short cervix or an open cervix (22% of study population) undergoing cerclage found no difference with progesterone and cerclage (prophylactic or emergency) compared with cerclage alone (odds ratio 2.83 (95% CI 0.58 to 13.89)).

Tocolysis

There is no role for tocolysis alone in women with an open cervix and exposed membranes in the absence of uterine activity.

Tocolytics have been given as an adjunct to ECC in RCT but their role as an intervention has not been individually assessed.[6]

Box End

Is ongoing research likely to provide relevant evidence?

We searched ISRTCN, PROSPERO, and NIHR registries for ongoing studies on emergency cervical cerclage. We found two ongoing randomised controlled trials in the United Kingdom.

We are conducting the C-STICH2 trial to assess effect of ECC on pregnancy loss in singleton pregnancies (50 women), the risks of ECC, and maternal and neonatal outcomes over a two year follow-up. An accompanying prospective observational cohort study (120 women) will inform on the incidence of the condition.

ENCIRCLE aims to assess the effect of ECC on time to delivery, preterm birth, pregnancy loss, and maternal and neonatal outcomes in (*a*) women with a twin pregnancy with an open cervix and exposed fetal membranes and (*b*) women with a short cervix after laser treatment for twin-to-twin transfusion syndrome. ENCIRCLE aims to recruit 31 women.

There are no registered trials assessing progesterone, antibiotics, or bed rest for women with an open cervix and exposed fetal membranes.

Box Start

Recommendations for further research

- Effectiveness of emergency cervical cerclage (ECC) in earlier or later gestations (than 16-28 weeks), and in women with different causes for preterm birth (multiple pregnancies, structural uterine anomalies, previous full dilatation caesarean section, or cervical surgery)
- Women's views and experiences on options for prevention and management of preterm birth to develop optimal care pathways

• Future studies must report on all preterm birth core outcomes and include long term follow-up of surviving children.

Box End

What should we do in light of the uncertainty?

This is a challenging emergency to manage with a high risk of a poor outcome for mothers and babies and few proven effective treatments.

Women, their partners, and families must be offered counselling by a consultant obstetrician and paediatrician, taking into consideration the woman's wishes, to choose between expectant management or bed rest and emergency cervical cerclage. It is important that they receive information about possible outcomes of the condition, interventions, and potential adverse effects for mother and baby. A calculation tool has been developed based on the results of a previous RCT to demonstrate graphically to women and clinicians the likelihood of reaching specific gestations dependent on the timing of intervention.

Antibiotics may be used if urinary tract infection or chorioamnionitis is suspected or confirmed. Women with exposed membranes may have increased risk of subclinical infection within the amniotic fluid (microbial invasion of the amniotic cavity). This is thought to cause some cases of painless cervical dilatation,[9] but it is not routinely investigated (by amniocentesis) or treated.

ECC is not available within all maternity settings due to local policies and availability of experienced practitioners. We recommend establishing local networks such that women can be offered appropriate interventions regionally.

Box Start

What patients need to know

• Sometimes the neck of the womb can start to open early and the bag of waters around the baby can come through the neck of the womb (fig 1).

• If this happens too early in pregnancy (before 28 weeks), there are a limited number of options to prolong the pregnancy. These include expectant management or bed rest (combined sometimes with antibiotics, progesterone, or medicines to stop the womb contracting) or emergency cervical cerclage (ECC).

• An ECC is the placement of a stitch around the neck of the womb after replacement of the bag of waters.

• There is some evidence from small studies that ECC may prolong pregnancy, preventing some of the complications of being born too early. The evidence is of low quality, and there are no long term data on pregnancy outcomes in the mother and newborn.

Box End

Date search

We searched the ISRTCN, PROSPERO, and NIHR research registries to identify any ongoing studies.

Search strategy

We searched the Cochrane Library for systematic reviews on emergency cervical cerclage, progesterone, tocolysis, and bed rest.

When there was no Cochrane review, we searched for systematic reviews, randomised control trials, or observational studies in PubMed.

Query results

- ((open cervix) OR (cervical dilatation) OR (exposed fetal membranes)) AND (bedrest)—33 results
- ((open cervix) OR (cervical dilatation) OR (exposed fetal membranes)) AND (progesterone)—159 results
- ((open cervix) OR (cervical dilatation) OR (exposed fetal membranes)) AND (cervical pessary)—77 results
- ((open cervix) OR (cervical dilatation) OR (exposed fetal membranes)) AND (antibiotics)—190 results
- (physical exam indicated cerclage) OR (emergency cervical cerclage)—277 results

Box End

Box Start

Education into practice

- How would you discuss management options with pregnant women at risk of preterm birth?
- How would you ensure your practice is linked with local or regional maternity services that offer emergency cervical cerclage?

Box End

Box Start

How patients were involved in the creation of this article

We asked a patient representative on our trial group to contribute to this paper. The patient representative has contributed extensively in the context of the trial regarding use of language and what parents wish to know, and has reviewed the manuscript to ensure the language used is supportive and appropriate and parent's priorities are addressed.

Box End

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