

OBSTETRICS

A randomized controlled trial of cervical scanning vs history to determine cerclage in women at high risk of preterm birth (CIRCLE trial)

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OBJECTIVE: We sought to compare history-indicated placement of cervical cerclage based on history- vs ultrasound-indicated placement in women at risk of preterm birth.

STUDY DESIGN: We conducted a randomized controlled trial of history-indicated cervical cerclage suture based on history (clinician preference) vs ultrasound (< 20 mm cervical length) indicated in women at increased risk.

RESULTS: The incidence of the primary outcome, preterm delivery between 24⁺⁰ and 33⁺⁶ weeks, was similar: 19/125 (15%) in the his-

tory-indicated group vs 18/122 (15%) in the ultrasound-indicated group (relative risk [RR], 0.97; 95% confidence interval [CI], 0.54-1.76). Those women randomized to the ultrasound-indicated arm were significantly more likely to receive a cerclage (32% vs 19%; RR, 1.66; 95% CI, 1.07-2.47) and progesterone (39% vs 25%; RR, 1.55; 95% CI, 1.06-2.25).

CONCLUSION: Screening women at high risk with cervical ultrasound to determine cerclage placement results in more intervention but similar outcome compared with history-indicated placement.

Key words: cerclage, cervical scanning, preterm birth

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Preterm delivery (PTD), defined as the birth of an infant before 37 completed weeks of gestation, is the single most important determinant of neonatal morbidity and mortality.¹ The incidence ranges from approximately 5-12%, and is increasing globally.^{1,2} Preterm labor has multiple and potentially overlapping causes. Primary dysfunction of the cervix probably plays a role in the etiology of some, but not the majority, of cases of preterm birth.³ However, whatever the cause of the onset of parturition, the final common pathway is cervical shortening and dilatation; hence cervical cerclage may be helpful either as a preventative or

therapeutic measure in preventing PTD.⁴ Identifying those individuals who may benefit from cerclage requires accurate prediction of women at risk. The majority of those who deliver preterm in their first pregnancy subsequently deliver at term in the next pregnancy⁵ and previous randomized controlled trials of history-indicated or prophylactic cerclage only alters outcome in a minority of cases.⁴ On the basis of currently available data it is recommended that history-indicated cerclage is only placed in women with multiple pregnancy losses, although most women who deliver preterm do not have such a history. Cervical

length determined by ultrasound has been used as a risk assessment for spontaneous PTD; the relative risk of a preterm birth increases with shortening cervical length.⁶ Measuring cervical length in a woman with a previous preterm birth could help to more appropriately target those needing intervention.

It has been suggested that targeting the ultrasonographically short cervix with cerclage may reduce the need for history-indicated procedures^{7,8} but the ability of ultrasound to reduce the risk of preterm birth by also identifying those who do not receive cerclage based on history (eg, only 1 previous PTD) has not been tested. We, therefore, undertook a randomized trial in asymptomatic women at high risk, who had at least 1 previous delivery between 16 and 34 weeks, to compare ultrasound-indicated cervical cerclage for those with a short cervix, with elective management with no ultrasound scans, in which the decision to place a prophylactic history-indicated suture was based on the obstetric history alone. Because obstetric history is a poor predictor of subsequent pregnancy outcome and it is likely that the majority of cervical sutures are inserted unnecessar-

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ily, it was hypothesized that ultrasound scanning of the cervix would identify those women who would benefit most from cerclage, preventing unnecessary procedures in women at very high risk while identifying those who otherwise would not receive a cerclage.

MATERIALS AND METHODS

Eligibility

Pregnant women at $< 24^{+0}$ weeks of gestation were recruited to the study during a 2.5-year period from November 2003 through March 2006 from 9 United Kingdom hospitals. Eligibility criteria included singleton pregnancy with at least 1 previous spontaneous delivery between 16^{+0} and 34^{+0} weeks of gestation. Woman unable to give informed consent were excluded. Ethical approval was obtained from the Trent Multicenter Research Ethics Committee and all participating centers' local research ethics committees. The trial was conducted according to the written protocol that had been approved by multicenter research ethics committee. The randomization sequence was computer generated in balanced block multiples. Stratification was performed to control for gestation of last delivery before 24 weeks. Allocation was made by telephone to the central trials office in London, United Kingdom.

Women allocated to the scanning arm of the trial underwent cervical length assessment by transvaginal ultrasound every 2 weeks from entry into the trial until 24^{+0} weeks of gestation. If the cervix shortened to ≤ 20 mm, a cervical cerclage was inserted. Cervical measurement continued postcerclage up to 24^{+0} weeks. For those women allocated to the history-indicated arm of the trial, a history-indicated suture was offered if the treating clinician considered that the obstetric history justified a cerclage. There were no proscribed minimum criteria for history-indicated suture insertion. The decision to insert a cerclage or not, based on history, was made in every case before randomization by the attending clinician, and then carried out if the patient was randomized to the history arm.

In both groups the technique and type of material used for the procedure was at

the discretion of the obstetrician. Similarly, additional treatments such as antibiotics, tocolysis, steroid prophylaxis, and the use of bed rest were not dictated by the trial protocol, but evaluated as secondary outcomes. Suture removal was carried out in week 37 of pregnancy unless there was a clinical indication to remove earlier.

Data collection and analysis

Data were recorded using a trial-specific collection form and clinical outcome information was collected from maternity records and hospital computer databases. Analysis was by intention to treat. The primary outcome measure was PTD before 34 weeks. Main secondary outcome measures were frequency of suture insertion, incidence of histologic chorioamnionitis, incidence of maternal pyrexia, hospital admissions, bed rest, and the use of steroids, tocolysis, and progesterone. Neonatal outcome measures were needed for oxygen therapy at 28 days and ultrasound evidence of brain abnormality.

Statistical analysis

A power calculation determined that 250 women would be needed to be able to demonstrate (with 90% power, at a 5% significance level) that the treatment effect would be no more than from a 40% incidence to $> 20\%$ incidence in early delivery before 34 weeks' gestation, assuming that ultrasound-indicated cerclage has no additional beneficial effect. The χ^2 or Fisher exact tests with 2-sided *P* values were used to compare categorical outcomes between the 2 groups. As there were no substantial or significant differences at baseline between the groups, no adjustments were made for confounding. For those outcomes that were continuous variables, either a parametric *t* test or Mann-Whitney nonparametric test was used, depending on the distribution of the data. Economic data (time of hospital stay), where the mean difference is of particular interest, was estimated with a 95% confidence interval (CI) and *P* value based on bootstrap resampling with 10,000 replications.

RESULTS

In all, 253 women were randomized to the trial. Three were subsequently identified as not fitting eligibility criteria and a further 2 were excluded from analysis as they elected to terminate the pregnancy after diagnosis of a fetal anomaly: 1 trisomy 21, terminated at 21^{+5} weeks, and 1 fetal hydrops, terminated at 12^{+0} weeks (neither had entered the treatment protocol before pregnancy termination).

Of 248 women, 123 were assigned to the ultrasound scanning group and 125 to history-indicated management group. There was no difference in the gestational age at entry to trial. Progress of the participants through the trial is described in Figure 1. Primary outcome data were available on 247/248 women (99.6%).

One woman in each arm declined a suture; in the scanning arm, the woman delivered at 26^{+2} weeks, and in the history arm, the woman delivered at term. There were 9 patients who did not receive the randomized intervention. Eight women in the history arm were scanned; 3 were found to have a cervix < 20 mm and had a suture inserted. One woman in the scanning arm needed an ultrasound-indicated suture in a previous pregnancy and changed her mind, requesting a history-indicated suture in the current pregnancy. She delivered at 39^{+1} weeks. All analysis was conducted according to the original allocation, following the intention-to-treat principle.

The demography and baseline risk data are described in Table 1. There are no substantial or significant differences between the randomized groups.

The incidence of PTD at between 24^{+0} and 33^{+6} weeks of gestation (the primary outcome) was similar between the 2 groups: 19/125 (15%) in the history-indicated management group vs 18/122 (15%) in the scanning group (relative risk [RR], 0.97; 95% CI, 0.54-1.76). Differences in loss before 24 weeks were not significantly different (12 [10%] in the history-indicated and 4 [3.3%] in the scanning groups; RR, 0.34; CI, 0.11-1.02), although the study was underpowered to show significant differ-

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