Cerclage suture type to prevent pregnancy loss in women requiring a vaginal cervical cerclage: the C-STICH RCT

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Scientific summary

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Scientific summary

Background

Preterm birth and second trimester miscarriage is a significant cause of worldwide neonatal morbidity and mortality. The aetiology is complex and multifactorial with a number of causes, including cervical insufficiency. One treatment to prevent preterm birth and second trimester miscarriage caused by cervical insufficiency is the placement of a vaginal cervical cerclage (CC). A CC is the placement of a purse string suture thread around the cervix aiming to prevent pregnancy loss and preterm birth. A CC can be performed with either a monofilament suture thread or a braided suture thread. The choice of thread used during surgical operations is dependent on the properties of the thread, with braided threads being multifilament in nature with lots of single strands woven together, which predisposes it to potentially becoming colonised with pathogenic bacteria. A prior feasibility study suggested a difference in pregnancy loss outcomes between monofilament and braided suture threads and the acceptability of either thread for clinicians and women. Therefore, a randomised controlled trial was designed to explore this discrepancy, aiming to reduce pregnancy loss for women at high risk of preterm birth.

Objectives

The primary objective of the study was to examine the effectiveness of using a monofilament suture material compared to a braided suture material on minimising the risk of pregnancy loss in women requiring a vaginal CC. The secondary objectives of the study included exploring the impact of suture material on maternal and neonatal outcomes.

Design

A pragmatic open, parallel, multicentre, randomised superiority trial of monofilament versus braided suture type during CC to prevent pregnancy loss.

Setting

The study was conducted in hospital settings across the UK (75 sites) between 2015 and 2022.

Participants

Women were eligible for the trial if they required a vaginal CC as part of their routine care within their current pregnancy and they fulfilled the following eligibility criteria:

Inclusion

- Singleton pregnancy.
- Indication for CC for either:
  - a history of three or more previous mid-term losses or premature births (≤ 28 weeks), OR
  - insertion of cervical sutures in previous pregnancies, OR
  - a history of mid-trimester loss or premature birth with a shortened (≤ 25 mm) cervix, OR
  - women whom clinicians deemed to be at risk of preterm birth either because of their history or because of the results of an ultrasound scan.

Exclusion

- Had taken part in C-STICH previously.
- Aged < 18 years old at the time of presentation.
- Requiring a rescue cerclage.
- Unwilling or unable to give informed consent.
- Those in whom a cerclage was to be placed by any route other than vaginally (e.g. via an abdominal route).
- Immediate need for insertion of a suture.
- Membranes that had ruptured or were surfacing.

Interventions

Women were randomised at a 1 : 1 ratio via a secure internet facility to have their CC performed using either a monofilament or braided suture thread. Minimisation was employed to balance for the following: indication for cerclage, planned bladder dissection, intention to commence patient on progesterone and recruiting site.

Outcome measures

The primary outcome measure was pregnancy loss (miscarriage and perinatal mortality).

Key secondary outcome:

- Time from conception to pregnancy end (any reason).

Maternal outcomes:

- Miscarriage and previable neonatal death (defined as delivery < 24 weeks).
- Stillbirth (defined as intrauterine death ≥ 24 weeks).
- Gestation at delivery (in live births ≥ 24 weeks).
- Gestational age of < 28/< 32/< 37 weeks at delivery (in live births ≥ 24 weeks).
- Time from conception to onset of spontaneous vaginal delivery (in live births ≥ 24 weeks).
- Sepsis (at any time in pregnancy and until 7 days postnatal).
- Preterm prelabour rupture of membranes (PPROM).
- Mode of initiation of labour (spontaneous or induced).
- Mode of delivery (vaginal, operative vaginal or caesarean).
- Cerclage placement complications (cervical laceration/bleeding from cervix/ruptured membranes/bladder injury).
- Cerclage removal complications (cervical tears/need for anaesthetic/difficult to remove).
- Other maternal complications: vaginal bleeding/steroid use/chorioamnionitis/maternal pyrexia of 38°C (intrapartum/postnatal)/admission to high dependency unit (HDU) or intensive therapy unit (ITU) (pre/post delivery).

Neonatal outcomes:

- Early neonatal death (defined as a death within 7 days after delivery) (in live births ≥ 24 weeks).
- Late neonatal death (defined as a death beyond 7 days and before 28 days after delivery) (in live births ≥ 24 weeks).
- Birth-weight centile adjusted for gestational age and sex (in live births ≥ 24 weeks).
- Small for gestational age and sex (< 10th centile, in live births ≥ 24 weeks).

- Resuscitation at birth (in live births ≥ 24 weeks).
- Additional care required [special care baby unit (SCBU)/neonatal intensive care unit (NICU)/HDU/transitional care] and length of stay in additional care (in live births ≥ 24 weeks).
- Antibiotics within 72 hours (in live births ≥ 24 weeks).
- Sepsis (clinically diagnosed/proven) (in live births ≥ 24 weeks).
- Early neurodevelopmental morbidity (severe abnormality on cranial ultrasound scan) (in live births ≥ 24 weeks).
- Respiratory support and days on respiratory support (in live births ≥ 24 weeks).
- Supplementary oxygen requirements at 36 weeks post menstrual age (in live births ≥ 24 weeks).
- Necrotising enterocolitis (Bell's stage 2 or 3) (in live births ≥ 24 weeks).
- Retinopathy of prematurity requiring laser treatment (in live births ≥ 24 weeks).
- Disabilities (live births ≥ 24 weeks).
- Congenital anomalies (in live births ≥ 24 weeks).

The core outcome set for preterm birth was fully collected within the trial.

Sample size

The original sample size was based on a meta-analysis of non-randomised studies, where the pooled pregnancy loss rate in the monofilament group was 7% compared to 19% in the braided group. To allow for the observational nature of these data, we powered the study to detect a more plausible relative reduction of 41% (19% with braided sutures to 11.2% with monofilament sutures) with 90% power (alpha = 0.05). We planned to recruit 900 women. As a result of some uncertainty around the sample size parameters, the data monitoring committee reviewed the pooled event rate throughout the study. The sample size was subsequently increased to 2050 women to allow for a lower-than-anticipated event rate in order to maintain sufficient power to detect the same relative risk reduction. The primary analysis was by intention to treat.

Results

The trial opened for recruitment in August 2015 and completed recruitment in January 2021. A total of 2049 women were randomised into the trial and data for analysis was available for 1003 women in the monofilament group and 993 women in the braided group. The baseline demographic characteristics of women in the monofilament and braided group were similar. There was no evidence of a difference in pregnancy loss rates between the monofilament and braided groups [80/1003 vs. 75/993; adjusted risk ratio (RR) 1.05, 95% confidence interval (CI) 0.79 to 1.40; adjusted risk difference 0.002, 95% CI −0.02 to 0.03]. There was no difference in conception to pregnancy end (median time to pregnancy end: 37.9 weeks vs. 38.0 weeks; adjusted hazard ratio 1.04, 95% CI 0.95 to 1.14). Regarding maternal outcomes there was a decrease in maternal sepsis in the monofilament group (4%) compared to the braided group (7%) (RR 0.58, 95% CI 0.40 to 0.82) and a decreased risk of chorioamnionitis in the monofilament group (3%) compared to the braided group (6%) (RR 0.45, 95% CI 0.29 to 0.71). There was no difference in any neonatal outcomes. CC removal complications showed an increase in the monofilament group (56% vs. 42%, RR 1.25, 95% CI 1.15 to 1.36), with increased difficulty of removal and an increased need for anaesthetic for removal being the most common complications.

Conclusions

There was no evidence of a difference between a monofilament suture thread and a braided suture for pregnancy outcomes. We can be relatively confident that using a monofilament suture is unlikely to have a substantial impact on pregnancy loss compared to a braided suture. The uncertainty around our

comparative estimate for this outcome is at most 2% in favour of the monofilament in absolute terms. While this margin may not completely rule out missing a clinically important difference, we consider this scenario to be unlikely. Therefore, clinicians should consider the relative merits and disadvantages of the physical suture properties when selecting the material to perform a vaginal CC. The trial was robustly conducted with minimal limitations. An important strength of the study is the recognition early in the trial that the event rate was lower than anticipated and, therefore, the sample size was increased allowing the effectiveness of a monofilament versus braided suture thread to be fully evaluated.

Trial registration

This trial is registered as ISRCTN15373349.

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