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Monofilament suture versus braided suture thread to improve pregnancy outcomes after vaginal cervical cerclage (C-STICH): a pragmatic randomised, controlled, phase 3, superiority trial

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Summary

Background Miscarriage in the second trimester and preterm birth are significant global problems. Vaginal cervical cerclage is performed to prevent pregnancy loss and preterm birth. We aimed to determine the effectiveness of a monofilament suture thread compared with braided suture thread on pregnancy loss rates in women undergoing a cervical cerclage.

Methods C-STICH was a pragmatic, randomised, controlled, superiority trial done at 75 obstetric units in the UK. Women with a singleton pregnancy who received a vaginal cervical cerclage due to a history of pregnancy loss or premature birth, or if indicated by ultrasound, were centrally randomised (1:1) using minimisation to receive a monofilament suture or braided suture thread for their cervical cerclage. Women and outcome assessors were masked to allocation as far as possible. The primary outcome was pregnancy loss, defined as miscarriage, stillbirth, or neonatal death in the first week of life, analysed in the intention-to-treat population (ie, all women who were randomly assigned). Safety was also assessed in the intention-to-treat population. The trial was registered with ISRCTN, ISRCTN15373349.

Findings Between Aug 21, 2015, and Jan 28, 2021, 2049 women were randomly assigned to receive a monofilament suture (n=1025) or braided suture (n=1024). The primary outcome was ascertained in 1003 women in the monofilament suture group and 993 women in the braided suture group. Pregnancy loss occurred in 80 (8·0%) of 1003 women in the monofilament suture group and 75 (7·6%) of 993 women in the braided suture group (adjusted risk ratio 1·05 [95% CI 0·79 to 1·40]; adjusted risk difference 0·002 [95% CI –0·02 to 0·03]).

Interpretation Monofilament suture did not reduce rate of pregnancy loss when compared with a braided suture. Clinicians should use the results of this trial to facilitate discussions around the choice of suture thread to optimise outcomes.

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Introduction

Preterm birth is a significant global problem, complicating approximately 10% of all pregnancies.[1] The consequences of preterm birth can be clinically significant, with some babies being born too early to survive and survivors experiencing lifelong complications, such as cerebral palsy.[2] The causes of preterm birth are complex and multifactorial.[3] One cause is cervical insufficiency, occurring in 0·5–1·0% of pregnant women, for which the placement of a vaginal cervical cerclage is a potential treatment. Indications for cervical cerclage include a history of previous second trimester miscarriage or preterm birth, previous cervical surgery, or short cervical length identified by transvaginal ultrasound assessment of the cervix.[4,5] Two techniques can be used to perform a vaginal cervical cerclage: a modifed Shirodkar cerclage, which involves the dissection of the bladder with suture placement around the supravaginal cervix with the suture thread buried, or a McDonald cerclage, which involves a purse-string insertion as high as feasible around the upper section of the vaginal cervix.[6]

Perioperative decisions during vaginal cervical cerclage have the potential to alter the effectiveness of the intervention[7]—eg, suture thread choice is one such decision. Both monofilament and multifilament (braided) threads are commonly used to perform a cerclage. A previous UK survey highlighted that 87% of clinicians preferred to use a braided thread, with 13% of clinicians preferring monofilament.[8] This preference for braided suture was largely associated with ease of

Research in context

Evidence before this study

We searched MEDLINE, EMBASE, CINHL, and ISRCTN from database inception to Feb 2, 2013, without language restrictions, using the search terms "Cerclage", "cervix", "suture", and "Mersilene suture". Our search was continuously updated during the lifetime of the trial. No randomised controlled trials comparing suture material in relation to planned or elective cerclage were identified. Extending the searches to non-randomised studies identified observational studies that showed a reduction in neonatal death and preterm birth from 18% when a braided suture was used to 7% when a monofilament suture was used in a cervical cerclage. Additionally, evidence suggested a multifilament (braided) suture thread at cervical cerclage caused significant disruption to the vaginal microbiome with loss of lactobacillus dominance. These observational data supported the hypothesis that braided sutures are predisposed to infection causing pregnancy loss and prematurity.

Added value of this study

This is the first randomised controlled trial to assess the effect on pregnancy loss of using a monofilament suture thread compared with braided suture thread. The robustness of the study design and high rates of retention ensured internal validity and enabled the findings to be interpreted with confidence. Groups were balanced with respect to intention to dissect the bladder during the cerclage procedure, intended or current progesterone use, and clinical indication for cerclage, variables which are potentially prognostic for the likelihood of success with a vaginal cervical cerclage. The pragmatic design included a range of indications for cervical cerclage (excluding emergency) and reflected the diversity of current UK practice, increasing the generalisability of the results.

Implications of all the available evidence

We conclude that in women who require a vaginal cervical cerclage, a monofilament suture provides no additional benefit compared with a braided suture for the primary outcome of pregnancy loss.

handling and concerns regarding monofilament sutures becoming embedded in the cervix and becoming difficult to remove.[8]

Observational evidence from a non-randomised systematic review suggested a benefit of using a monofilament suture compared with a braided suture in preventing pregnancy loss (7·0% *vs* 18·9%; risk ratio [RR] 0·34 [95% CI 0·18–0·63]).[9,10] Consistent with this observational evidence, additional research supported the hypothesis that monofilament sutures might be superior to braided suture threads since braided threads could act as a reservoir for pathogenic bacteria, causing vaginal dysbiosis and increasing the risk of pregnancy loss.[5] This hypothesis was supported by microbiome studies, in which monofilament sutures were shown to reduce vaginal dysbiosis, thereby preventing a microbiome shift to pathogenic bacteria and improving maternal and neonatal outcomes through the prevention of infection. No evidence from any randomised controlled trials is available to inform suture thread choice for vaginal cervical cerclage to prevent pregnancy loss.

The aim of the C-STICH study was to compare the effect of monofilament suture with braided suture on rates of pregnancy loss in women requiring a vaginal cervical cerclage.

Methods

Study design

We did a multicentre, randomised, pragmatic, superiority trial at 75 obstetric units in the UK. Ethics approval for the trial was obtained from the Cambridge and Hertfordshire Research Ethics Service Committee (REC no 14/EE/1293). The full methods and trial protocol have been published previously.[11]

Participants

Eligible participants were women requiring a vaginal cervical cerclage as part of their standard care. Women aged 18 years or older with a singleton pregnancy and an indication for cervical cerclage were eligible for inclusion. An indication for cerclage was defined as either a history of three or more previous mid-term losses or premature births (≤28 weeks), insertion of cervical sutures in previous pregnancies, a history of mid-trimester loss or premature birth, with a shortened cervix (≤25 mm) in the current pregnancy, or clinician concern for risk of preterm birth either due to history or the results of an ultrasound scan. Women were excluded if they had been included in C-STICH previously; required an emergency or rescue cerclage; needed immediate insertion of a suture; or had membranes that had ruptured or were visible. Women in whom a cerclage was to be placed by any route other than vaginally (eg, via an abdominal route) were also excluded. All participants provided written informed consent. No gestational age limits were applied for consent, randomisation, or placement of the cervical cerclage.

Randomisation and masking

Participants were randomly assigned (1:1) to receive a monofilament or braided suture for their cervical cerclage. Randomisation was done via a secure online randomisation system, with the use of minimisation to balance trial group assignments according to planned

bladder dissection (yes or no), intention to commence patient on progesterone or current use (yes or no), indication for cerclage (a history of ≥3 previous mid-term losses or premature births [≤28 weeks], insertion of cervical sutures in previous pregnancies, a history of mid-trimester loss or premature birth with a current shortened cervix [≤25 mm], or clinician concern for risk of preterm birth either due to history or the results of an ultrasound scan), and by recruiting site. The randomisation system was provided centrally by the Birmingham Clinical Trials Unit. The clinicians performing the vaginal cervical cerclage could not be masked to the suture thread, and the surgical record documented the type of cerclage inserted and surgical techniques. Women and other research staff (eg, microbiologists, outcome assessors) were masked to treatment allocation as far as possible.

Procedures

The pragmatic trial design encouraged surgeons who performed the vaginal cervical cerclage to use their preferred surgical technique, with all perioperative steps at their discretion. Only the suture material was prespecified as per the randomised allocation. Where possible, use of Mersilene (Ethicon, Raritan, NJ, USA; non-absorbable and composed of polyethylene terephthalate) was encouraged for the braided suture and Ethilon (Ethicon; non-absorbable and composed of long-chain aliphatic polymers of nylon) was encouraged for the monofilament suture.

Women were followed up until 28 days post-delivery or discharge to home (whichever occurred first). Surviving neonates who were born preterm (gestational age <37 weeks) were followed up until their estimated date of delivery or discharge to home (whichever occurred first). Babies born at term were followed up until 28 days post-delivery or discharge to home (whichever occurred first).

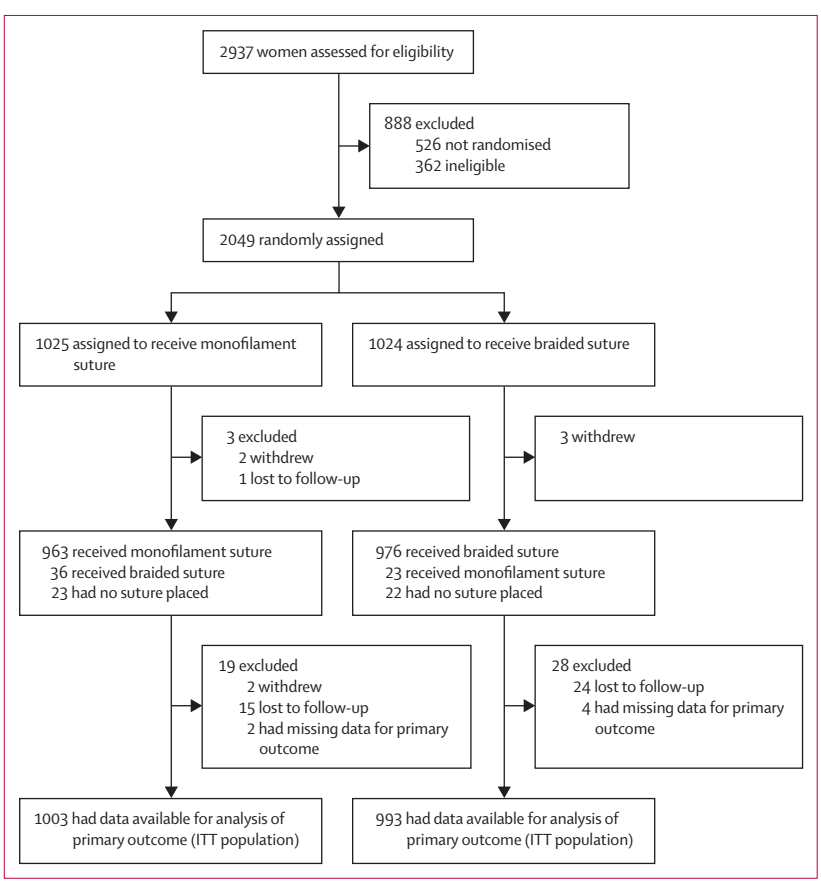

Figure 1: **Trial profile**
ITT=intention-to-treat.

Outcomes

The primary outcome was pregnancy loss, defined as miscarriage and perinatal mortality, including any stillbirth or neonatal death in the first week of life. Secondary outcomes included all outcomes in the core outcome set for preterm birth.[12] A key secondary outcome was time from conception to pregnancy end (any reason). Secondary maternal and pregnancy outcomes were miscarriage and previable neonatal death (defined as delivery <24 weeks), stillbirth (defined as intrauterine death ≥24 weeks), gestation at delivery (including <28, <32, and <37 weeks in livebirths born ≥24 weeks), time from conception to onset of spontaneous vaginal delivery (in livebirths ≥24 weeks), sepsis (at any time in pregnancy and until 7 days postnatal) defined as infection plus any two systemic manifestations of infection from the following: fever (≥38°C) or hypothermia (<36°C), tachycardia (heart rate >90 beats per min), tachypnoea (respiratory rate >20 breaths per min), preterm prelabour rupture of membranes, 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, or bladder injury), cerclage removal complications (cervical tears, need for anaesthetic, or difficulty removing suture), and other maternal complications (including vaginal bleeding, steroid use, chorioamnionitis, maternal pyrexia, and admission to high dependency unit or intensive care unit [ICU] in the intrapartum and postnatal period). Secondary neonatal outcomes were early neonatal death (defined as a death within 7 days after delivery), late neonatal death (defined as a death more than 7 days and less than 28 days after delivery), birthweight centile adjusted for gestational age and sex, small for gestational age and sex (<10th centile), resuscitation at birth, additional care required (admission to special care baby unit, neonatal ICU, high dependency unit, or transitional care) and length of stay in additional care, antibiotics within 72 h, sepsis (clinically diagnosed or microbiologically proven), early neurodevelopmental morbidity (severe abnormality on cranial ultrasound scan), respiratory support and days on respiratory support, supplementary oxygen requirements at 36 weeks postmenstrual age, necrotising enterocolitis (Bell's stage 2 or 3), retinopathy of prematurity requiring laser treatment,

	Monofilament suture (n=1025)	Braided suture (n=1023*)
Participant characteristics		
Gestational age at randomisation, weeks	16·5 (3·7)	16·6 (3·8)
Maternal age, years	32·8 (5·0)	33·0 (5·1)
Ethnicity		
White	592 (58·1%)	566 (55·8%)
Asian	197 (19·3%)	196 (19·3%)
Black	181 (17·8%)	205 (20·2%)
Mixed	36 (3·5%)	37 (3·7%)
Other	13 (1·3%)	10 (1·0%)
Data missing	6 (0·6%)	9 (0·9%)
BMI at booking appointment, kg/m²†	27·2 (6·3)‡	28·1 (6·5)§
Pregnancy history		
Gravida	2·0 (1·0–4·0)	2·0 (1·0–4·0)
Parity		
Nulliparous	307 (30·0%)	309 (30·2%)
1–3	661 (64·5%)	661 (64·6%)
>3	57 (5·6%)	53 (5·2%)
Median	1·0 (0–2·0)	1·0 (0–2·0)
First trimester losses	0 (0–1·0)	0 (0–1·0)
Mid-trimester losses	1·0 (0–1·0)	1·0 (0–1·0)
Termination of pregnancies	0 (0–0)	0 (0–0)
Livebirths (born ≤33^{+6} weeks)	0 (0–1·0)	0 (0–1·0)
Livebirths (born between ≥34 and <37 weeks)	0 (0–0)	0 (0–0)
Livebirths (born ≥37 weeks)	0 (0–1·0)	0 (0–1·0)
Clinical characteristics		
Cervical length ultrasound scan performed	709 (69·2%)	718 (70·2%)
Shortest cervical length before cerclage, mm¶	23·2 (9·8)	23·1 (9·0)
Cervical funnelling¶		
Yes	239 (33·7%)	248 (34·5%)
No	419 (59·1%)	435 (60·6%)
Not known	51 (7·2%)	35 (4·9%)
Primary indication for cerclage‖		
Deemed risk of preterm birth through history or ultrasound	620 (60·5%)	619 (60·5%)
Insertion of cervical sutures in previous pregnancies	219 (21·4%)	220 (21·5%)
History of mid-trimester loss or premature birth with a shortened cervix	164 (16·0%)	160 (15·6%)
History of ≥3 previous mid-term losses or premature births	22 (2·2%)	24 (2·4%)
Planned cerclage technique includes bladder dissection‖	174 (17·0%)	175 (17·1%)
Intention to commence on progesterone‖	415 (40·5%)	414 (40·5%)
Previous cervical surgery	258 (25·7%)	280 (28·1%)
Data missing	19 (1·9%)	28 (2·7%)
(Table 1 continues in next column)		

	Monofilament suture (n=1025)	Braided suture (n=1023*)
(Continued from previous column)		
Type of previous cervical surgery**		
One previous large loop excision of the transformation zone	123 (48·1%)	131 (46·8%)
Two previous large loop excisions of the transformation zone	45 (17·6%)	53 (18·9%)
Knife cone biopsy	29 (11·3%)	32 (11·4%)
Other††	59 (23·1%)	64 (22·9%)
Data missing	2 (<1·0%)	0
Prophylactic antibiotics at cerclage insertion‡‡	471 (48·9%)	466 (48·3%)
Data missing	35 (3·5%)	35 (3·5%)

Data are mean (SD), n (%), or median (IQR). Denominators for complete data were calculated excluding missing data.*Excluding the woman who was randomised in error, since no data were collected. †BMI data only available on version 2.0 (or newer) of the cerclage placement form. ‡Data were missing for 678 women. §Data were missing for 686 women. ¶In women who had a cervical length ultrasound scan. ‖Minimisation variable. **Among women with a history of previous cervical surgery. ††Other includes >2 large loop excisions of the transformation zone, large loop excision of the transformation zone and cone biopsies, >1 cone biopsy, myomectomies, cervical sutures, biopsies, vaginal trachelectomy for cervical cancer, cauterisation, colposcopies, bicornuate uterus and uterine septum hysteroscopically resected, cold coagulation, cryotherapy, laser treatment, removal of polyps, post-coital tear repair, and removal of uterine septum. ‡‡In women who had a cerclage placed and were recruited using version 2.0 (or newer) of the cerclage placement form.

Table 1: **Baseline characteristics of participants**

disabilities, and congenital anomalies. Serious adverse events were collected throughout the trial for both the mother and baby.

Statistical analysis

On the basis of previous meta-analyses,[9,11] we estimated that a sample size of 900 women was required to detect a relative risk reduction of 41% in the rate of pregnancy loss from 19·0% in the braided suture group to 11·2% in the monofilament suture group with 90% power at an α level of 0·05, including inflation to allow for an estimated attrition rate of 2·5%. This sample size was conservative to allow for the inherent risk of bias of observational studies, which would likely exaggerate the size of any treatment effect. Considering the uncertainty around the estimates used for the rates of pregnancy loss, the data monitoring committee monitored the pooled group event rate and in July, 2017, advised that the sample size should be increased due to a lower event rate than anticipated. This change was implemented on March 5, 2018. To detect the same relative reduction, assuming a pooled pregnancy loss rate of 7·4%, a revised sample size of 2050 women was agreed (equivalent to 9·3% in the braided suture group and 5·5% in the monofilament suture group, with all other original parameters remaining fixed). The pooled event rate and calculation were not disclosed to the trial management group.

	Monofilament suture	Braided suture	Estimate (95% CI)	RD (95% CI)
Pregnancy loss	80/1003 (8·0%)	75/993 (7·6%)	RR 1·05* (0·79 to 1·40)	0·00† (–0·02 to 0·03)
Median time from conception to pregnancy end, weeks (IQR; n)	37·9 (35·6–39·1; n=1008)	38·0 (35·4–39·1; n=998)	HR 1·04‡ (0·95–1·14)	..
Miscarriage or previable neonatal death	60/1003 (6·0%)	49/993 (4·9%)	RR 1·21§ (0·84–1·74)	0·01† (–0·01 to 0·03)
Stillbirth	8/1003 (<1·0%)	11/993 (1·1%)	RR 0·72§ (0·29 to 1·77)	0·00¶ (–0·01 to 0·01)
Mean gestational age at delivery, weeks (SD; n)‖	37·2 (3·3; n=926)	37·2 (3·4; n=919)	0·02** (–0·29 to 0·32)	..
Gestational age at delivery <28 weeks‖	34/926 (3·7%)	35/919 (3·8%)	RR 0·96†† (0·61 to 1·53)	0·00¶ (–0·02 to 0·02)
Gestational age at delivery <32 weeks‖	77/926 (8·3%)	86/919 (9·4%)	RR 0·89§‡‡ (0·66 to 1·19)	–0·01††‡ (–0·03 to 0·02)
Gestational age at delivery <37 weeks‖	258/926 (27·9%)	265/919 (28·8%)	RR 0·96§‡‡ (0·83 to 1·11)	–0·01††‡ (–0·05 to 0·03)
Median time from conception to onset of spontaneous vaginal delivery, weeks (IQR; n)§§	37·9 (35·6–39·4; n=342)	38·0 (35·7–39·6; n=342)	HR 1·07‡ (0·91 to 1·26)	..
Maternal sepsis	39/1000 (3·9%)	67/988 (6·8%)	RR 0·58* (0·40 to 0·82)	–0·03† (–0·05 to –0·01)
Preterm prelabour membrane rupture	199/1006 (19·8%)	201/997 (20·2%)	RR 0·98§ (0·82 to 1·16)	–0·01† (–0·04 to 0·03)
Mode of initiation of birth				
Spontaneous	446/957 (46·6%)	437/951 (46·0%)	RR 0·99§ (0·91 to 1·07)	–0·01† (–0·05 to 0·04)
Induced	327/957 (34·2%)	338/951 (35·5%)	..	..
Caesarean section	184/957 (19·2%)	176/951 (18·5%)	..	..
Mode of delivery				
Vaginal	490/953 (51·4%)	513/943 (54·4%)	RR 0·94¶¶ (0·86 to 1·02)	–0·03‖‖ (–0·08 to 0·01)
Operative vaginal	112/953 (11·8%)	81/943 (8·6%)	..	..
Caesarean delivery	351/953 (36·8%)	349/943 (37·0%)	..	..
Vaginal bleeding	142/995 (14·3%)	154/988 (15·6%)	RR 0·91* (0·74 to 1·12)	–0·01† (–0·04 to 0·02)
Steroid use	294/1000 (29·4%)	303/993 (30·5%)	RR 0·97§ (0·85 to 1·10)	–0·01† (–0·05 to 0·03)
Chorioamnionitis	26/956 (2·7%)	57/957 (6·0%)	RR 0·45* (0·29 to 0·71)	–0·03¶ (–0·05 to –0·01)
Maternal pyrexia (intrapartum)	22/1003 (2·2%)	35/992 (3·5%)	RR 0·62* (0·37 to 1·05)	–0·01† (–0·03 to 0·00)
Maternal pyrexia (postnatal)	44/1001 (4·4%)	44/989 (4·5%)	RR 0·98* (0·65 to 1·48)	0·00† (–0·02 to 0·02)
Admission to high dependency unit (pre-delivery)	17/1003 (1·7%)	21/996 (2·1%)	RR 0·80* (0·43 to 1·51)	–0·01† (–0·02 to 0·01)
Admission to ICU (pre-delivery)	0/1002	1/995 (<1·0%)	..	..
Admission to high dependency unit (post-delivery)	52/999 (5·2%)	50/986 (5·1%)	RR 1·02* (0·70 to 1·49)	0·00† (–0·02 to 0·02)
Admission to ICU (post-delivery)	1/998 (<1·0%)	5/986 (<1·0%)	RR 0·20§ (0·02 to 1·69)	0·00¶ (–0·01 to 0·00)

Data are n/N (%), unless otherwise specified. RR=risk ratio. RD=risk difference. HR=hazard ratio. ICU=intensive care unit. *Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, intention to commence on progesterone, and centre; values <1 favoured monofilament suture thread. †Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <0 favoured monofilament suture thread. ‡Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, intention to commence on progesterone, centre, and gestational age; values <1 favoured monofilament suture thread. §Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <1 favoured monofilament suture thread. ¶Unadjusted estimate (adjustment variables removed from the model due to convergence issues); values <0 favoured monofilament suture thread. ‖In livebirths ≥24 weeks. **Mean difference adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, intention to commence on progesterone, centre, and gestational age; values >0 favoured monofilament suture thread. ††Unadjusted estimate (adjustment variables removed from the model due to convergence issues); values <1 favoured monofilament suture thread. ‡‡Further adjusted for gestational age at randomisation. §§In livebirths ≥24 weeks who had a spontaneous vaginal delivery (monofilament suture N=342; braided suture N=342). ¶¶Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values >1 favoured monofilament suture thread (vaginal delivery *vs* operative vaginal or caesarean delivery). ‖‖Adjusted for the minimisation parameters: primary indication for cerclage, planned cerclage technique includes bladder dissection and intention to commence on progesterone (centre removed from the model due to convergence issues); values >0 favoured monofilament (vaginal delivery *vs* operative vaginal or caesarean delivery).

Table 2: **Pregnancy and maternal outcomes**

A comprehensive statistical analysis plan was specified before analysis. The primary outcome was analysed in the intention-to-treat population (ie, all randomly assigned participants). All estimates of differences between groups were presented with two-sided 95% CIs adjusted for the minimisation variables (where convergence was possible). Time from conception to pregnancy end, gestational age at delivery, and time from conception to onset of spontaneous vaginal delivery were further adjusted for gestational age at randomisation.

The primary outcome was analysed using a mixed-effects log-binomial model to generate an adjusted RR

and risk difference (RD; using an identity link function), including centre as a random effect. Statistical significance of the treatment group parameter was determined through examination of the associated χ^2 statistic (obtained from the model that produced the RR). A hierarchical approach to testing was planned to control for the overall rate of type I error; if the primary outcome met the criteria for superiority, then the key secondary outcome (time from conception to pregnancy end) would also be tested using this approach. No formal hypothesis tests were performed for any other secondary outcomes.

Binary maternal outcomes and three binary neonatal outcomes (early neonatal death, late neonatal death, and small for gestational age) were analysed as per the primary outcome, but were not subjected to hypothesis testing. For continuous secondary outcome measures (birthweight centile and gestational age at delivery), adjusted mean differences were estimated using a linear regression model, including centre as a random effect. Time-to-event outcomes were analysed using Cox regression models. Cerclage placement complications, cerclage removal complications, and all other neonatal outcomes were only analysed descriptively, unless overall event rates exceeded 3%, then formal analysis was done as per the binary secondary outcomes. Safety was analysed in the intention-to-treat population, with the exception of adverse events associated with cerclage placement or removal, which could only be analysed in women who had a cerclage placed or removed.

Sensitivity and supportive analyses of the primary outcome included a per-protocol analysis, including only women regarded as adherent, an as-treated analysis, whereby women were analysed as per suture thread used for their first cervical cerclage. We also did an analysis to investigate missing primary outcome data by means of a so-called tipping-point approach, which explored the possibility that missing responses were missing not at random. We did prespecified subgroup analyses (limited to the primary outcome measure only) for the following: planned bladder dissection (yes or no), intention to commence patient on progesterone or current use (yes or no), indication for cerclage (a history of three or more previous mid-term losses or premature births [≤28 weeks], insertion of cervical sutures in previous pregnancies, a history of mid-trimester loss or premature birth with a current shortened cervix [≤25 mm], or clinician concern for risk of preterm birth either due to history or the results of an ultrasound scan). The effects of these subgroups were examined by adding the subgroup by treatment group interaction parameters to the regression model. p values from the tests for statistical heterogeneity were presented with the effect estimate and estimates of uncertainty within each subgroup. Additionally, ratios were provided to quantify the difference between the treatment effects estimated within each subgroup.

All analyses were performed in SAS (version 9.4) or Stata (version 17.0). A trial steering committee provided independent oversight of the trial. Confidential inspection of all available data alongside anonymised reports of serious adverse events experienced by participants were reviewed by a data monitoring committee; no reason to recommend halting the trial was identified. This trial is registered with ISRCTN, ISRCTN15373349.

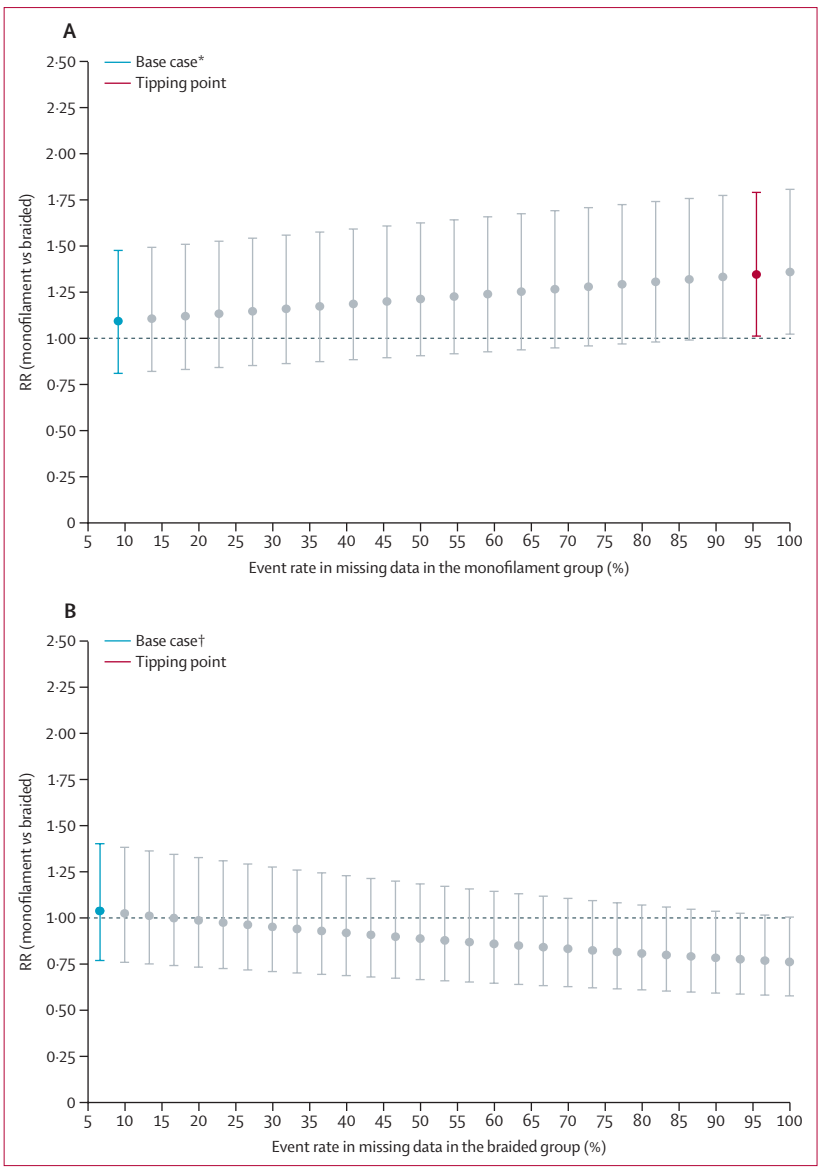

Figure 2: **Tipping-point analysis for assessment of missing data in the monofilament suture group (A) and braided suture group (B)**

RRs <1 favoured the monofilament suture. RR=risk ratio. *Estimate derived from the model where the event rate in the missing data was assumed to be equal to the event rate in the non-missing data in the monofilament suture group; all missing data in the braided suture group were assumed to be non-events. †Estimate derived from the model where the event rate in the missing data was assumed to be equal to the event rate in the non-missing data in the braided suture group; all missing data in the monofilament suture group were assumed to be non-events.

Role of the funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, writing of

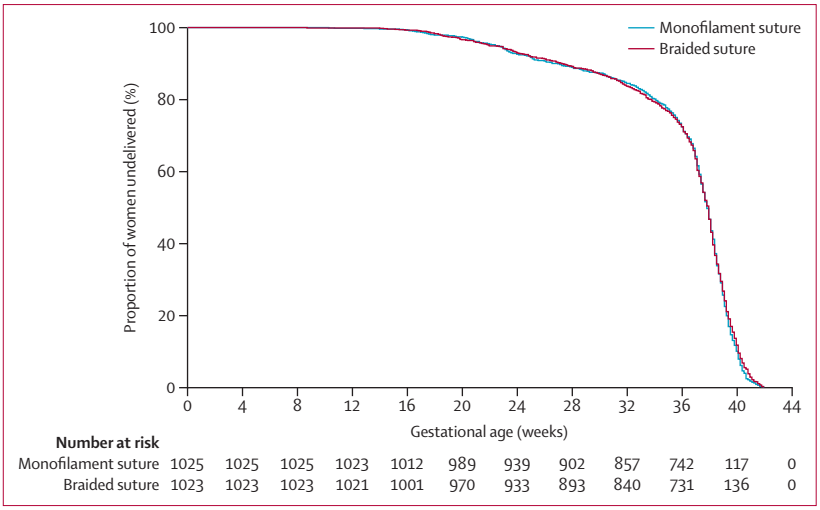

Figure 3: **Kaplan-Meier plot of time from conception to pregnancy end by intervention group.**

the report, or decision to submit the results for publication.

Results

Between Aug 21, 2015, and Jan 28, 2021, 2937 women were screened for eligibility, of whom 2049 were randomly assigned to the monofilament suture thread group (n=1025) or the braided suture thread group (n=1024; figure 1). Withdrawal rates and loss to follow-up were similar across both groups.

At enrolment, baseline characteristics were balanced between groups (table 1). The mean age was 32·9 years (SD 5·0), mean BMI at time of booking appointment was 27·7 kg/m², and 1158 (56·5%) of 2048 women were White. The cervical cerclage was placed in 1998 (97·8%) of 2043 women, and 963 (94·2%) of 1022 women in the monofilament suture group and 976 (95·6%) of 1021 women in the braided suture group received the suture type they had been randomly allocated (figure 1). 1003 women in the monofilament suture group and 993 women assigned to the braided suture group had available data for primary outcome analysis, and thus were included in the intention-to-treat analysis.

We found no statistically significant difference in the primary outcome between the groups. 80 (8·0%) of 1003 women in the monofilament suture group and 75 (7·6%) of 993 women in the braided suture group had pregnancy loss (adjusted RR 1·05 [95% CI 0·79 to 1·40]; adjusted RD 0·002 [95% CI –0·02 to 0·03]; p=0·73; table 2). Sensitivity and supportive analyses had minimal impact on effect estimates (appendix p 1). For the tipping-point analysis, which assessed the impact of missing primary outcome data, if it was assumed that no cases of pregnancy loss occurred in women with missing data in the braided suture group, we needed to assume more than 95% of the women with missing data in the monofilament suture group had pregnancy loss to change the conclusion of the outcome (in favour of a braided suture). Conversely, if it was assumed that no cases of pregnancy loss occurred in women with missing data in the monofilament suture group and we assumed all women with missing data in the braided suture group had pregnancy loss, the conclusion of the outcome would not change in favour of a monofilament suture (figure 2).

See Online for appendix

For the key subgroup of planned bladder dissection, there was evidence of a potential differential treatment effect ($p_{interaction}$=0·05; appendix pp 2–3), but estimates within each subgroup did not differ significantly.

No statistically significant differences were identified in the maternal secondary outcomes, with the exception of maternal sepsis and chorioamnionitis, for which incidence was lower in the monofilament suture group than the braided suture group (RR 0·58 [95% CI 0·40–0·82] for maternal sepsis; RR 0·45 [95% CI 0·29–0·71] for chorioamnionitis; table 2). Median time from to conception to pregnancy end was 37·9 weeks (IQR 35·6–39·1) in the monofilament suture group and 38·0 weeks (IQR 35·4–39·1) in the braided suture group (figure 3). There was no evidence of a difference between any of the neonatal outcomes (table 3), and the trial was not powered to detect differences in these outcomes.

43 (4%) of 999 women in the monofilament suture group and 30 (3%) of 999 women in the braided suture group had insertion complications (table 4). Bleeding from the cervix was the most common complication; two women in the monofilament suture group had ruptured membranes during cervical cerclage insertion. More women in the monofilament suture group than the braided suture group experienced removal complications (RR 1·25 [95% CI 1·15–1·36]). Removal complications included clinician-judged difficulty in suture removal and an increased need for anaesthetic; 382 (41%) of 934 women in the monofilament suture group required an anaesthetic for removal compared with 293 (32%) of 922 women in the braided suture group. 108 (11%) of 1025 women and eight (1%) of 1025 neonates in the monofilament suture group and 99 (10%) of 1023 women and 19 (2%) of 1023 neonates in the braided suture group had serious adverse events. Nine women and one neonate in the monofilament suture group and three women in the braided suture group had a related unexpected serious adverse event, the majority of which were related to cerclage insertion and removal complications (appendix p 2). All other serious adverse events were not considered related to the allocated intervention or were expected outcomes of the condition.

Discussion

C-STICH was designed to investigate whether the use of a monofilament suture thread was superior to a braided suture thread in reducing pregnancy loss rates when

	Monofilament suture (n=926)	Braided suture (n=919)	Estimate (95% CI)	Risk difference (95% CI)
Early neonatal death (<7 days)	5/920 (<1·0%)	3/913 (<1·0%)	RR 1·63* (0·39 to 6·80)	0·00† (0·00 to 0·01)
Late neonatal death (≥7 to <28 days)	1/920 (<1%)	0/913	..	..
Mean birthweight centile (SD; n)	41·0 (29·2; n=923)	42·4 (28·8; n=912)	−1·44‡ (−4·09 to 1·21)	..
Small for gestational age (<10th centile on population chart)	147/923 (15·9%)	132/912 (14·5%)	RR 1·10§ (0·84 to 1·45)	0·02¶ (−0·02 to 0·05)
Resuscitation at birth	61/916 (6·7%)	62/911 (6·8%)	RR 0·98* (0·70 to 1·38)	0·00¶ (−0·02 to 0·02)
Additional care	265/920 (28·8%)	268/912 (29·4%)	RR 0·98* (0·85 to 1·13)	0·00¶ (−0·05 to 0·04)
Median length of stay in additional care, days (IQR; n)				
Special care baby unit	4·0 (0–15·0; n=243)	4·0 (0–16·0; n= 258)	..	..
Neonatal ICU	0 (0–7·0; n= 231)	0 (0–6·0; n=247)	..	..
High dependency unit	0 (0–4·0; n=233)	0 (0–4·0; n=244)	..	..
Transitional care	0 (0–1·5; n=220)	0 (0–1·0; n= 241)	..	..
Antibiotics within 72 h after birth	236/915 (25·8%)	249/906 (27·5%)	RR 0·94§ (0·81 to 1·09)	−0·01¶ (−0·06 to 0·03)
Sepsis (clinically diagnosed)	102/909 (11·2%)	113/904 (12·5%)	RR 0·90§ (0·71 to 1·14)	−0·01¶ (−0·04 to 0·02)
Sepsis (microbiologically confirmed)	15/908 (1·7%)	19/904 (2·1%)	..	..
Early neurodevelopmental morbidity	13/912 (1·4%)	19/903 (2·1%)	..	..
Respiratory support	130/915 (14·2%)	144/910 (15·8%)	RR 0·90§ (0·72 to 1·11)	−0·01¶ (−0·05 to 0·02)
Median time on respiratory support, days (IQR; n)	5·0 (1·0–28·0; n= 125)	4·0 (1·0–27·0; n= 142)	..	..
Supplementary oxygen requirements	27/910 (3·0%)	30/914 (3·3%)	RR 0·91* (0·54 to 1·52)	0·00¶ (−0·02 to 0·01)
Necrotising enterocolitis (Bell's stage 2 or 3)	7/908 (<1·0%)	11/909 (1·2%)	..	..
Retinopathy of prematurity requiring laser treatment	4/906 (<1%)	5/908 (<1·0%)	..	..
Disabilities	1/910 (<1·0%)	5/904 (<1·0%)	..	..
Congenital anomalies	18/914 (2·0%)	18/909 (2·0%)	..	..
Chromosomal abnormalities	2 (<1·0%)	4 (<1·0%)	..	..
Cleft lip and cleft palate	3 (<1·0%)	3 (<1·0%)	..	..
Congenital malformations and deformations of the musculoskeletal system	5 (<1·0%)	4 (<1·0%)	..	..
Congenital malformations of genital organs	2 (<1·0%)	0	..	..
Congenital malformations of the circulatory system	5 (<1·0%)	5 (<1·0%)	..	..
Congenital malformations of the digestive system	2 (<1·0%)	0	..	..
Congenital malformations of the nervous system	0	1 (<1·0%)	..	..
Congenital malformations of the urinary system	1 (<1·0%)	2 (<1·0%)	..	..

In livebirths ≥24 weeks. Data are n/N (%), unless otherwise specified. RR=risk ratio. ICU=intensive care unit. *Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <1 favoured monofilament suture thread. †Unadjusted estimate (adjustment variables removed from the model due to convergence issues); values <0 favoured monofilament suture thread. ‡Mean difference adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, intention to commence on progesterone, and centre; values >0 favoured monofilament suture thread. §Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, intention to commence on progesterone, and centre; values <1 favoured monofilament suture thread. ¶Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <0 favoured monofilament suture thread.

***Table 3*: Neonatal outcomes**

performing a vaginal cervical cerclage in women deemed to be at high risk of preterm birth or pregnancy loss during the second trimester. Our hypothesis was that a braided suture would act as a reservoir for bacteria that would increase the clinical infection rate or severity of infection leading to increased pregnancy loss. Overall, we found no significant difference in the primary outcome of pregnancy loss between the groups. We can now be relatively confident that use of a monofilament suture is unlikely to have a substantial effect on pregnancy loss or gestational age at delivery compared with a braided suture.

	Monofilament suture	Braided suture	RR (95% CI)	RD (95% CI)
Cerclage complications				
Cerclage placement complication*	43/999 (4·3%)	30/999 (3·0%)	1·44† (0·91 to 2·27)	0·01‡ (0·00 to 0·03)
Details of cerclage placement complications*				
Cervical laceration	5/999 (<1·0%)	2/999 (<1·0%)	..	..
Bleeding from cervix	39/999 (3·9%)	29/999 (2·9%)	..	..
Ruptured membranes	2/999 (<1%)	0	..	..
Bladder injury	0	0	..	..
Cerclage removal complication§	506/896 (56·5%)	373/883 (42·2%)	1·25† (1·15 to 1·36)	0·14¶ (0·10 to 0·18)
Details of cerclage removal complications§				
Cervical tears	20/863 (2·3%)	8/865 (<1·0%)	..	..
Difficulty in removal	276/885 (31·2%)	128/875 (14·6%)	..	..
Need for anaesthetic	382/934 (40·9%)	293/922 (31·8%)	..	..
Adverse events				
Number of women with serious adverse events	108/1025 (10·5%)	99/1023‖ (9·7%)	..	..
Maternal serious adverse events, n	126	115	..	..
Number of neonates with serious adverse events	8/1025 (<1·0%)	19/1023‖ (1·9%)	..	..
Neonatal serious adverse events, n	15	25	..	..
Number of women with a related unexpected serious adverse event	6/1025 (<1·0%)	3/1023‖ (<1·0%)	..	..
Number of maternal related unexpected serious adverse events, n	9	3	..	..
Number of neonates with a related unexpected serious adverse event	1/1025 (<1%)	0/1023‖	..	..
Number of neonatal related unexpected serious adverse events	1	0	..	..

Data are n/N (%), unless otherwise specified. RR=risk ratio. *Cervical laceration, bleeding from cervix, ruptured membranes, or bladder injury in women who had a cerclage placed. †Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <1 favoured monofilament suture thread. ‡Unadjusted estimate (adjustment variables removed from the model due to convergence issues); values <0 favoured monofilament suture thread. §Cervical tears, difficulty removing the cerclage, or need for anaesthetic in women who confirmed their cerclage was removed (monofilament suture n=964, braided suture n=956; these denominators for women who had cerclage removal differ from those provided in the table for cerclage removal complications because some women did not answer questions about cerclage removal complications). ¶Adjusted for the minimisation parameters: primary indication for cerclage, intention to dissect the bladder during cerclage placement, and intention to commence on progesterone (centre removed from the model due to convergence issues); values <0 favoured monofilament suture thread. ||Excluding the woman who was randomised in error since no data were collected.

Table 4: **Serious adverse events and cerclage placement and removal complications**

With regard to the secondary outcomes, decreased risk of maternal sepsis was identified in the monofilament suture group (4%) compared with the braided suture group (7%) and a decreased risk of clinical chorioamnionitis (3% in the monofilament suture group *vs* 6% in the braided suture group); however, the trial was not powered to detect differences in these outcomes. The decreased risk of infection in the monofilament suture group is consistent with the hypothesis that braided sutures might be reservoirs for bacteria that predispose to infection.[9]

No differences in neonatal outcomes were identified between the two groups. The neonatal outcomes collected in this trial are rare neonatal outcomes mainly related to prematurity, and the trial was not powered to detect differences between the two groups for these outcomes. Maternal chorioamnionitis is associated with an increased risk of both early and late neonatal sepsis;[13] however, no difference in clinically diagnosed neonatal sepsis was identified between the monofilament suture group (11%) and the braided suture group (13%). No difference was identified in the proportion of neonates with confirmed neonatal sepsis. The proportion of neonates who required antibiotics was high in both groups (26–27%). The longer-term neonatal consequences of chorioamnionitis are unclear, with some studies reporting an increased risk of adverse neonatal complications and others demonstrating no difference, and with some studies only finding a link between histologically confirmed chorioamnionitis and worsening infant neurodevelopmental outcomes.[14] There is some evidence that chorioamnionitis in combination with prematurity confers an increased risk of cerebral palsy and worse neurodevelopmental outcomes, which is particularly important among women who require a cervical cerclage.[14] Additionally, maternal chorioamnionitis is associated with increased incidence of adverse events among mothers, including increased risk of haemorrhage, blood transfusion, and higher rates of complications from caesarean sections and intensive care admissions.[15] The high incidence of infections observed in our trial might be

a consequence of bias. The outcome assessors within the trial might have been aware of the suture material used because the intervention could not be masked and, considering the acknowledged concern that braided sutures might result in a higher incidence of infection and the relative subjectivity of some of these outcomes, there might have been a tendency to make a diagnosis of infection in the braided suture group. This potential for bias could seem more likely considering the paucity of evidence that any of the known consequences of infection, either for the mother or the baby, were significantly increased in the braided suture group. We can be confident that the primary outcome of pregnancy loss is not associated with detection bias, but some of the secondary outcomes might have been susceptible to this bias.

There was a subjective increase in difficulty removing a monofilament suture, with additional requirement for anaesthesia at removal. This should also be interpreted with the knowledge that, in contrast to the insertion of cerclages (performed by specialists), a wide range of clinicians typically remove cerclages—and thus these clinicians might have less experience with removal of monofilament sutures than braided sutures because monofilament sutures are not as commonly used. Additionally, this outcome might also have been influenced by detection bias.

We did not collect long-term data and are therefore unable to draw any conclusions about the differential effect of maternal infection rates on long-term neurodevelopmental outcomes or maternal morbidity. There is an opportunity within C-STICH to seek funding to evaluate longer term maternal and paediatric outcomes and this should be prioritised.

Before this trial, a substantial amount of observational evidence indicated that monofilament sutures might reduce pregnancy loss and prevent prematurity, potentially as a result of less disruption of the vaginal microbiome. There are several reasons why this effect might not have been demonstrated in C-STICH—for example, clinicians in the observational study might have been more experienced, leading to potentially better clinical outcomes related to skill level rather than suture thread; they might also have been aware of the hypothesised drawbacks of a braided suture and therefore preferred a monofilament thread. C-STICH was a pragmatic study in which cervical cerclages were placed by clinicians who would routinely perform this procedure, and this is an important strength of this trial.

This was a well designed trial done across a large maternity network (75 sites) with a pragmatic study entry criterion, in which a diverse and representative population was recruited; therefore, the findings are generalisable to worldwide practice. Our study findings have important implications for practice regarding suture thread choice. When surgical procedures are evaluated within all trials, variables such as suture thread must be considered and where reasonable, stratification used to prevent chance imbalance in groups. C-STICH demonstrates the importance of research to ensure that surgical techniques and operative decisions are fully evaluated before changes in practice occur based on observational evidence alone. Important limitations of this study include the short duration of follow-up for maternal and neonatal outcomes, with most neonatal outcomes relating to prematurity rather than infectious morbidity. There is an important opportunity to extend follow-up in this cohort for longer-term outcomes, which are especially important in trials relating to prematurity. Additionally, some outcomes might have been associated with detection bias due to the inability to mask clinicians and data collectors to the suture group allocation.

This trial aimed to establish whether the use of a monofilament suture material was superior to a braided suture material when performing a vaginal cervical cerclage for the prevention of pregnancy loss. The hypothesis of the trial was that braided sutures would harbour bacteria predisposing to infection, pregnancy loss, and premature birth. In conclusion, our results found no evidence of differences in rates of pregnancy loss between the suture groups. Clinicians should consider using a monofilament suture thread when performing a vaginal cervical cerclage, to reduce the risk of maternal sepsis and chorioamnionitis, due to the association of chorioamnionitis with adverse maternal outcomes.[13] Clinicians caring for women offered a vaginal cervical cerclage should use the result of this trial to facilitate discussions around the suture thread to optimise outcomes.

Contributors

PT-H was the chief investigator for the trial and conceived the project, supervised the COTS study, and was involved with the design, implementation, and oversight of the trial, and provided oversight of this manuscript. VHM was the research fellow on the trial and involved with the design, implementation, and recruitment to the trial, and wrote the manuscript. CAM was a trial statistician and was responsible for the analysis of the trial data and coauthored this manuscript. KT was a trial statistician and supported the setup of the trial. LM was the senior statistician for the trial and was responsible for the analysis of the trial data and coauthored this manuscript. JD was involved with the design of the trial, provided trial oversight, and critical review of the manuscript. AS and NABS were involved with recruitment to the trial and coauthored this manuscript. AKE was a coapplicant for the trial and was responsible for the design advising on neonatal outcomes and contributed to the critical review of the manuscript. MH was the trial coordinator. JG provided microbiological advice to the trial and coauthored the manuscript. PB provided senior input to the design of the trial and coauthored the manuscript. RKM provided senior input into the trial design and delivery and had oversight of the analysis. The corresponding author and trial statisticians had full access to all the data in the study and CM and LM verified the data. All authors in the writing team shared final responsibility for the decision to submit for publication.

Declaration of interests

VHM is a National Institute for Health and Care Research (NIHR) clinical lecturer and has received an honorarium from Hologic. JD reports membership of the NIHR Clinical Trials Unit Standing Advisory Committee (May 1, 2016, to Sept 30, 2023). JEN is a member of the Health Technology Assessment (HTA) Maternal, Neonatal and Child Health Panel; receives funding from NIHR Efficacy and Mechanism Evaluation programme; participates in a Data Monitoring and Ethics

Committee for GlaxoSmithKline; and is a paid consultant for DILAFOR. RKM receives funding from NIHR HTA and programme grants for Applied Health Research schemes; is a steering committee member of the Saving Babies Lives Care Bundle; and a paid Clinical Advisory Board member for Surepulse (a company designing neonatal monitors). All other authors declare no competing interests.

Data sharing

Requests for data should be directed to the corresponding author. Patient-level data will be made available within 6 months of publication. Requests will be assessed for scientific rigour before being granted. Data will be anonymised and securely transferred. A data-sharing agreement might be required.

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