

MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage

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Short Title: MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus
Transvaginal Cervical Cerclage

Research in Context

Evidence before this study

Vaginal cerclage is recommended in women with recurrent mid-trimester loss or early preterm birth. When vaginal cerclage fails, transabdominal cerclage has been advocated, with observational studies suggesting higher rates of success. We searched PubMed for original articles published in English prior to September 2018 with the search terms “spontaneous preterm birth OR cerclage OR transabdominal cerclage OR high vaginal cerclage”. There were no randomised studies which demonstrated benefit of abdominal versus repeat vaginal cerclage.

Added value of this study

This randomised controlled trial provides the first direct comparison of abdominal and high vaginal cerclage with low vaginal cerclage. Abdominal cerclage was demonstrated to be superior to low vaginal cerclage in women with prior failed cerclage in preventing early preterm birth (less than 32 weeks) and fetal loss. High vaginal cerclage was no better than low vaginal cerclage in preventing early birth.

Implications of all the available evidence

Women with a prior failed vaginal cerclage (pregnancy delivered before 28 weeks of gestation) should be offered an abdominal cerclage, either before or in early pregnancy.

ABSTRACT

Background

Vaginal cerclage (a suture around the cervix) is commonly placed in women with recurrent pregnancy loss. However these women may experience late miscarriage or extreme preterm delivery, despite being managed with cerclage. Transabdominal cerclage (TAC) has been advocated following failed cerclage, although its efficacy is unproven by randomised controlled trial (RCT).

Methods

A multicentre RCT to compare TAC or high vaginal cerclage (HVC) to low vaginal cerclage (LVC), as a preventative strategy for spontaneous preterm birth (sPTB) in women with history of a failed cerclage was undertaken. Women were randomly assigned (1:1:1) to receive TAC, HVC or LVC, either prior to conception or before 14 weeks' gestation. Primary outcome was delivery before 32 completed weeks of pregnancy.

Findings

111/139 women recruited who conceived were analysed: 39 to TAC, 39 to HVC and 33 to LVC. Rates of sPTB <32 weeks were significantly lower in women who received a TAC compared to LVC [8% (3/39) v 38% (15/39), RR 0.23 (95% CI 0.07 to 0.76), p=0.0078]. Number needed to treat (NNT) to prevent one sPTB was 3.9 (95% CI 2.2 to 13.3). There was no difference in sPTB rates between HVC and LVC [38% (15/39) vs 33% (11/33), RR 1.15 (95% CI 0.62 to 2.16),

p=0.81]. No neonatal deaths occurred. Women with TAC had fewer fetal losses, compared to LVC [3% (1/39) vs 21% (7/33), RR 0.12 (95% CI 0.016 to 0.93), p=0.02]. NNT to prevent one fetal loss was 5.3 (95% CI 2.9 to 26).

Interpretation

TAC is the treatment of choice for women with failed vaginal cerclage. It is superior to LVC in reducing risk of early preterm birth and fetal loss in women with previous failed vaginal cerclage. HVC does not confer this benefit. NNT are sufficiently low to justify transabdominal surgery and caesarean delivery required in this select cohort.

Funding

The trial was registered with the WHO International Clinical Trials Registry Platform (ISRCTN33404560) and funded by J P Moulton Charitable Foundation (Registered Charity No. 1109891). PTS is partly funded by Tommy's (Registered charity no. 1060508) and by CLAHRC South London (NIHR).

BACKGROUND

Recurrent late miscarriage and early preterm birth is often treated with vaginal cerclage (a suture placed around the cervix). This is known to have a significant benefit in a small number of cases probably representing those with genuine cervical incompetence, or who have traumatic cervical damage, such as that caused by surgery⁽¹⁾. When evaluated by randomised controlled trial (RCT), vaginal cerclage (VC) has limited value (1:25)⁽²⁾. Even without cerclage, most women will have a successful subsequent pregnancy. The challenge is to identify those women whose pregnancy losses are genuinely due to cervical weakness; women who experience multiple late miscarriages or early preterm births are more likely to fall into that category.

In women for whom vaginal cerclage fails, abdominal cerclage (TAC, inserted laparoscopically or via laparotomy) has been advocated but requires more extensive surgery than vaginal cerclage, and caesarean delivery. A number of observational series⁽³⁻⁶⁾ have suggested that abdominal cerclage is highly successful, however abdominal cerclage has never been evaluated in an RCT.

We hypothesised that abdominal cerclage (TAC) would result in lower rates of late miscarriage and early preterm delivery compared to low vaginal cerclage (LVC) by maintaining structural and biochemical integrity of the cervix because it is placed higher in the cervix, ideally at the level of the internal os. This may prevent the infective/inflammatory cascade associated with cervical shortening⁽⁷⁾, which may be due either to stretch of the fetal membranes as the internal os opens⁽⁸⁾, or loss of the cervical barrier to ascending infection⁽⁷⁾.

A VC can also be placed higher in the cervix, by mobilising the bladder (HVC). It is unknown whether this also results in lower rates of late miscarriage or PTB when compared to LVC.

METHODS

Study design and participants

The MAVRIC trial was a multicentre RCT funded by the J P Moulton Charitable Foundation, and supported by the NIHR Clinical Research Network (CRN). NHS Research Ethical Committee approval was obtained (REC 07/H1102/113) and the trial was registered on the International Standard Randomised Controlled Trial Registry (ISRCTN33404560).

Women were eligible for trial inclusion if they had a history of spontaneous late miscarriage or preterm birth before 28 completed weeks of pregnancy with low vaginal cerclage (LVC) in situ, but excluding rescue cerclage procedures, i.e. cerclage inserted with exposed membranes. Women were eligible for randomisation pre-conceptually or at less than 14 weeks' gestation.

Participants were referred from hospitals across the United Kingdom and recruited at 9 sites (London (4 sites), Kirkcaldy, Sunderland, Newcastle, Bradford and Edinburgh) between January 2008 and September 2014. All participants gave written informed consent, and were over the age of 16.

Procedures

Women with a previous failed cerclage were randomised to one of the following:

1. TAC: Transabdominal cerclage
2. HVC: High vaginal cerclage
3. LVC: Low vaginal cerclage

Techniques used were left to the local clinician's discretion. Details of surgical and anaesthetic technique were collected. Vaginal cerclage was inserted prior to 16 weeks' under regional anaesthetic and removed at 37 weeks' gestation, or earlier if preterm labour ensued. HVC involved mobilisation of the bladder from the anterior cervix allowing the suture to be placed higher, and usually required regional anaesthetic for removal. TAC was placed pre-conceptually or before 14 weeks' gestation under either regional or general anaesthetic, requiring inpatient stay of up to 3 days. Women with TAC were delivered by elective caesarean section at 38 to 39 weeks, with retention of the TAC for future pregnancies. All first trimester miscarriages (less than 13 weeks') post randomisation were excluded from the analysis (3 excluded: 1 in TAC, 1 in HVC and 1 in LVC group).

Randomisation and masking

Women enrolled in MAVRIC were randomly assigned to TAC, HVC or LVC (1:1:1) using a computer-generated randomisation procedure incorporated in an internet-based secure trial database (www.medscinet.net/MAVRIC). Minimisation was used to balance two prognostic variables: pregnancy at time of randomisation and gestational age of previous late miscarriage or preterm delivery (Table 1). Due to the nature of the interventions, treatment

allocation was known to both participants and health care professionals. Written informed consent was obtained from all participants and baseline demographic characteristics, risk factors and obstetric and gynaecologic history were entered into the study specific database.

Cerclage insertion was performed electively between 10 to 16 weeks' (14 weeks for TAC) or pre-conception if assigned to TAC or HVC, according to clinician and patient preference. All LVCs were carried out at the women's local maternity unit. As HVCs and TACs are more specialist procedures, these were carried out in one of the designated centres, to ensure a suitably experienced surgeon completed the procedure. Following cerclage insertion, women were monitored and managed according to local clinicians' practice. All care was in line with contemporaneous evidence-based guidelines.

Outcomes

Our primary outcome was delivery before 32 completed weeks of pregnancy, on which the trial was powered. Pre-defined secondary outcomes included neonatal death, serious operative complication rates and complications of pre- and post-conception cerclage (HVC and TAC).

Pregnancy outcomes were obtained from case note review, by trained research midwives. Women were considered to have had a spontaneous preterm birth (sPTB) if they had spontaneous onset of labour, or experienced preterm rupture of membranes and delivered prematurely, regardless of mode of delivery. There were no changes to pre-specified outcomes during recruitment. All pre-specified analyses were undertaken. As there were no

neonatal deaths, we compared the overall fetal loss rate by trial arm (composite of late miscarriage and stillbirth).

Sample size calculation

Sample size estimation was informed by data from an observational study by Davis *et al.* (4) the best available evidence at the time. Our primary outcome was rate of delivery before 32 complete weeks of gestation. Assuming a baseline event rate of 38% with LVC and 10% with TAC, a total of 43 women in each of the three groups (TAC, HVC and LVC) was required for 80% power, at the 5% significance level (2-tailed), to show a significant difference between LVC and the other two groups.

Statistical analysis

Statistical analyses were undertaken in Stata version 14.2 (StataCorp 15.1, College Station, Texas). Analysis was by intention to treat (pre-specified in the protocol), with planned comparison of treatment effects for binary endpoints using risk ratios and significance tests for both primary and secondary endpoints. We also performed a per protocol analysis, although this was not predefined.

RESULTS

Participants

This was a multicentre RCT, with patients as the unit of randomisation. The full study protocol can be found on the King's College London website (<https://www.kcl.ac.uk/lsm/research/divisions/wh/clinical/open/mavric.aspx>).

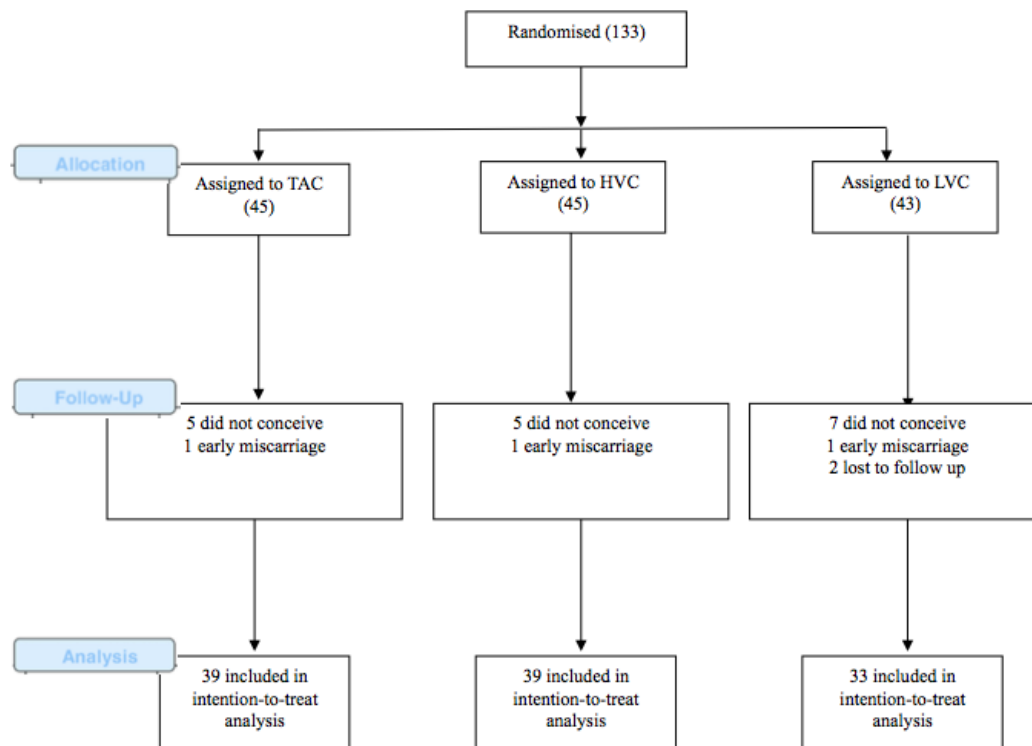


Figure 1: Participant flow chart with treatment allocation and exclusions

139 participants were recruited and randomly allocated a treatment. The first patient was recruited in January 2008. Recruitment ended in January 2014, when the planned recruitment target (n=129) had been exceeded. Seventy nine women were not pregnant at the time of randomisation, which was a higher number than anticipated. At this time 104 women had conceived. Four years later, only 7 additional women had conceived and delivered (1 in 2014, 4 in 2015 and 2 in 2017). Despite extensive efforts, we were unable to trace the outcomes of two participants who were known to have moved abroad. The data monitoring committee were consulted in September 2018; there had been no further conceptions during the

preceding 12 months, and therefore the decision was made to proceed with analysis. Analysis was performed on the 111 women with outcome data in September 2018.

	Transabdominal cerclage (39)	High vaginal cerclage (39)	Low vaginal cerclage (33)
	n (%)	n (%)	n (%)
Pregnant at randomisation	20 (44.4%)	16 (35.6%)	15 (34.9%)
Gestation at end of last pregnancy <24w	31 (68.9%)	26 (57.8%)	29 (67.4%)

Table 1: Variables used for minimisation by trial allocation following exclusions

Treatment allocation	Transabdominal (N=39)	High vaginal (n=39)	Low vaginal (n=33)	All (n=111)
	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)
Age at registration	31.9 (5.1)	32.1 (5.3)	31.8 (5.1)	32.3 (5.4)
BMI (kg/m ²)	29.9 (6.9)	30.1 (7.0)	29.9 (6.9)	30.1 (7.0)
Social class/occupation	n (%)	n (%)	n (%)	n (%)
Managerial/professional	12 (31%)	17 (44%)	13 (39%)	42 (38%)
Intermediate	20 (51%)	18 (46%)	14 (42%)	52 (47%)
Routine/unemployed	7 (18%)	4 (10%)	6 (18%)	17 (15%)
Ethnicity				
White	11 (28%)	10 (26%)	12 (36%)	33 (30%)
Black	21 (54%)	23 (59%)	18 (55%)	62 (56%)
Asian	4 (10%)	5 (13%)	3 (9%)	12 (11%)

Other	3 (8%)	1 (3%)	0 (0%)	4 (4%)
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Table 2: Maternal baseline demographic characteristics

Of the 111 participants who had conceived and with known outcome, 39 were randomised to TAC, 39 to HVC and 33 to LVC. Baseline demographic characteristics are shown in Table 2. Patients were managed as per local clinical practices: 17% (6/36) of women allocated to TAC were also prescribed progesterone, 28% (10/36) with HVC and 48% (14/29) with LVC. All women had a history of recurrent early delivery: the median number of late miscarriages was 2 (IQR 1 to 5) and preterm births were 1 (IQR 0 to 5).

Risk Factors	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)	All (n=111)
Cervical surgery	2 (5%)	6 (15%)	9 (27%)	17 (15%)
History of late miscarriage (mean, SD)	2.12 (1.15)	1.70 (1.12)	1.97 (1.08)	1.99 (1.15)
Range	0 - 5	0 - 4	0 - 5	1 to 5
History of early delivery (late miscarriage / PTB) (mean, SD)	2.73 (1.12)	2.65 (1.03)	2.91 (1.27)	2.76 (1.13)
Uterine anomaly	3 (8%)	4 (10%)	3 (9%)	10 (9%)
APS/Lupus antibodies	1 (3%)	2 (5%)	0 (0%)	3 (3%)
Smoked during pregnancy	3 (8%)	1 (3%)	4 (12%)	8 (7%)
Past or present history of:				

Recurrent UTIs (>2) in pregnancy	3 (8%)	4 (10%)	7 (21%)	14 (13%)
Group B Streptococcus	11 (28%)	10 (26%)	3 (9%)	24 (22%)
Bacterial Vaginosis	3 (8%)	4 (10%)	4 (12%)	11 (10%)
Recreational drug use	1 (3%)	0 (0%)	2 (6%)	3 (3%)
Domestic Violence	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3: Risk factors for spontaneous preterm birth

Outcomes

There was a statistically significant reduction in preterm birth less than 32 completed weeks' gestational age (the primary outcome) in women allocated to TAC compared to LVC [8% (3/39) v 38% (15/39), RR 0.23 (95% CI 0.07 to 0.76) p=0.0078]. There were no iatrogenic preterm deliveries among these women. Number needed to treat (NNT) to prevent one sPTB was 3.9 (95% CI 2.2 to 13.3). There was no difference in rates of sPTB between high and low VC [38% (15/39) vs 33% (11/33), RR 1.15 (95% CI 0.62 to 2.16), p=0.81]. TAC also demonstrated benefit when compared to HVC [8% (3/39) v 38% (15/39), RR 0.2 (95% CI 0.063 to 0.64), p=0.0024]. NNT was 3.2 (95% CI 2.0 to 7.4).

No neonatal deaths occurred. Women with a TAC had fewer fetal losses (late miscarriage or stillbirth), compared to LVC [3% (1/39) vs 21% (7/33), RR 0.12 (95% CI 0.016 to 0.93), p=0.02]. NNT to prevent one fetal loss was 5.3 (95% CI 2.9 to 26).

Treatment allocation	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)
Preterm (<32 weeks)*	3 (8%)	15 (38%)	11 (33%)

Preterm (<34 weeks)	4 (10%)	18 (46%)	13 (39%)
Preterm (<37 weeks)	11 (28%)	21 (54%)	17 (52%)
<i>*primary outcome</i>			
Live birth	38 (92%)	31 (79%)	26 (79%)
Late Miscarriage	1 (3%)	7 (18%)	7 (21%)
Stillbirth	0 (0%)	1 (3%)	0 (0%)
All fetal losses	1 (3%)	8 (21%)	7 (21%)

Table 4: Pregnancy outcome by randomised allocation

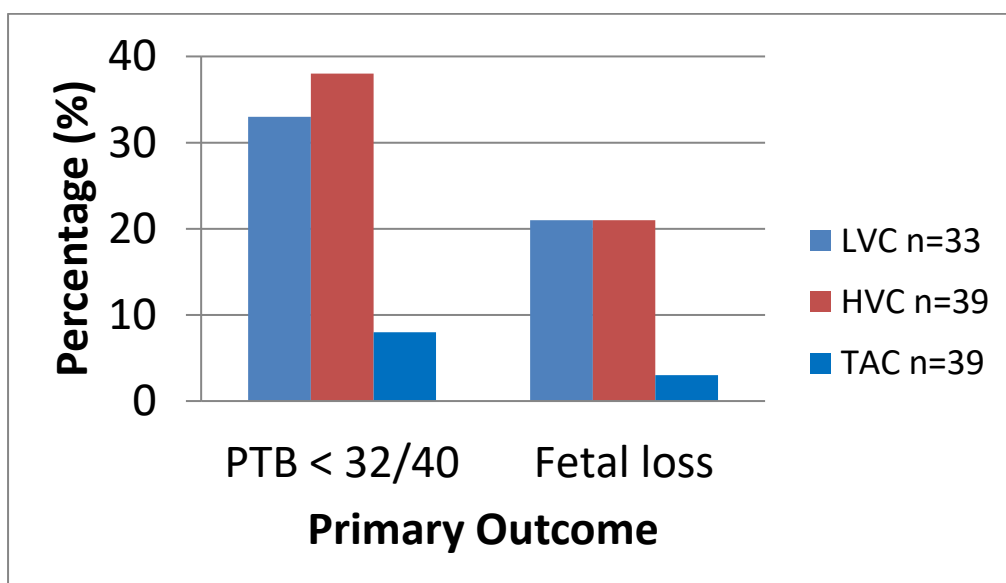


Figure 2: Primary outcome by treatment allocation

Serious morbidities were reported in four cases (2 x cervical tears, 1 x ITU admission with sepsis and 1 case of cardiomyopathy), all of which occurred in women with high (n=3) or low (n=1) vaginal cerclage. 6 women received a subsequent rescue cerclage (2 who were allocated HVC, 2 who were allocated LVC). Table 6 gives surgical and anaesthetic details for each

procedure divided by outcome; no specific trends are apparent and techniques are equally spread across the outcome groups.

	Preterm birth < 32 weeks		Baby loss	
	Intention to treat analysis	As per protocol analysis	Intention to treat analysis	As per protocol analysis
TAC versus LVC				
RR	0.23 (0.07 to 0.76) p=0.0078	0.21 (0.65 to 0.70) p=0.0059	0.12 (0.016 to 0.93) p=0.02	0.11 (0.014 to 0.86) p=0.018
TAC versus HVC				
RR	0.2 (0.063 to 0.64) p=0.0024	0.19 (0.058 to 0.59) p=0.001	0.13 (0.016 to 0.95) p=0.029	0.12 (0.015 to 0.88) p=0.012
HVC versus LVC				
RR	1.15 (0.62 to 2.16) p=0.81	1.15 (0.62 to 2.13) p=0.80	0.97 (0.39 to 2.38) p=1.00	0.96 (0.39 to 2.36) p=1.00

Table 7: Primary outcomes by intention to treat and as per protocol analysis

72% (28/39) of women with a TAC *in situ* delivered at term, compared to fewer than half of women with HVC (46%, 18/39) or LVC (48%, 16/33) (Table 4).

Eight women did not receive treatment as per allocation (see Table 5), as a result of patient choice following randomisation or treatment allocation being judged inappropriate, for example, the cervix was found to be too short on vaginal examination at time of procedure. Results are presented by intention to treat however, as shown in Table 7, were similar when analysed as per protocol.

ID	Randomisation	Final procedure	Gestation - details	Outcome
24	LVC	TAC	At 10 ⁺⁰ – patient preference	39 ⁺¹
56	LVC	TAC	Preconception - patient choice	36 ⁺⁰
66	LVC	HVC	At 14 ⁺⁰ – patient preference	37 ⁺⁵
79	HVC	TAC	At 12 ⁺⁵ – patient preference	38 ⁺⁶
87	TAC	LVC	At 10 ⁺⁶ – patient preference	38 ⁺⁰
88	LVC	TAC	10 ⁺² - No vaginal cervix on digital examination	37 ⁺⁶
111	TAC	HVC	13 ⁺³ - patient request	38 ⁺⁵
133	LVC	HVC	13 ⁺⁰ – transfer of care	38 ⁺²

Table 5: Details of patient crossovers from randomised allocation to treatment received

Procedure techniques	Transabdominal cerclage	High vaginal cerclage	Low vaginal cerclage
	(N=39)	(n=39)	(n=33)

	sPTB <32/40 (n=3)	Del >32/40 (n=36)	sPTB <32/40 (n=15)	Del >32/40 (n=24)	sPTB <32/40 (n=11)	Del >32/40 (n=22)
Regional Anaesthesia	0/3 (0%)	6/33 (18%)	14/15 (93%)	20/23 (87%)	11/11 (100%)	13/16 (81%)
Mersiline Tape*	1/3 (33%)	4/28 (14%)	12/13 (92%)	21/22 (95%)	9/10 (90%)	16/17 (94%)
>=2 sutures inserted	2/3 (66%)	18/28 (64%)	0/13 (0%)	1/22 (5%)	0/9 (0%)	0/17 (0%)
Cerclage tied anteriorly	0/3 (0%)	4/28 (14%)	13/13 (100%)	20/21 (95%)	10/10 (100%)	12/15 (80%)
Cerclage placed pre-conception	2/3 (66%)	18/36 (50%)	0/15 (0%)	0/24 (0%)	0/11 (0%)	0/22 (0%)
Subsequent rescue cerclage	0/3 (0%)	0/36 (0%)	3/15 (20%)	1/24 (4%)	2/11 (18%)	0/22 (0%)

Table 6: Details of surgical and anaesthetic techniques

*all other sutures were performed using monofilament suture

DISCUSSION

This is the first RCT comparing abdominal cerclage with vaginal cerclage. Our findings show that transabdominal cerclage is superior to low vaginal cerclage in preventing early PTB and fetal loss (late miscarriage and stillbirth). Compared to LVC, there was no benefit of HVC.

Numbers needed to treat were modest to both prevent delivery before 32 weeks (<4) and to prevent fetal loss (<6), and therefore the uptake of this procedure is likely to be efficient and cost effective. Further work should establish the health economic impact of such procedures including the longer-term need for caesarean sections and associated morbidity.

Although our numbers were small, they were based on an anticipated large treatment effect and we achieved the assumed event rates in our protocol, suggesting our findings are unlikely to be subject to a type 1 error. We had crossovers during the trial, but fewer than 10% of participants (8/111), and following a post-hoc per protocol analysis, the treatment effect was greater in favour of abdominal cerclage.

Women with failed cerclage are rare, and it is challenging to randomise such women into a trial where there are strong prior beliefs as to the perceived risk or benefit of the intervention and, therefore, lack of equipoise. This explains the length of time needed to reach the recruitment target, in spite of the national multicentre design. We found clinicians reluctant to randomise, with many unwilling to perform, and others unwilling to withhold an abdominal cerclage, even in the context of a trial. In addition, women who have experienced multiple pregnancy losses have often extensively researched the treatment options and have a fixed idea of which intervention would be best for them, so are unwilling to be randomised. We were unable to collect accurate screening data due to the referral nature of the trial.

We were underpowered to evaluate safety concerns and meaningful subgroup analysis was not possible. We were, therefore, unable to analyse complications pre- and post-conception with the abdominal procedure due to their rarity (none) and small numbers. No clinicians used laparoscopic TAC procedures and we therefore could not evaluate possible differences between this and other techniques. Other concerns related to abdominal cerclage include managing early miscarriage and infertility, were not apparent in this study. It is our experience, however, that evacuation of the uterus for missed miscarriage, or termination of pregnancy for fetal abnormality can be safely performed up to 14 weeks, leaving the abdominal cerclage in place.

Although the trial intended to evaluate rates of neonatal death, there were none. This suggests that women with a prior failed pregnancy before 28 weeks tend to have fetal losses at pre-viable gestations in the second trimester, if they recur. The mechanism of pregnancy failure causing late miscarriage and early preterm birth (resulting in neonatal death) is likely to be the same, and as we excluded early miscarriage, we therefore believe our fetal loss rates are a meaningful comparator across treatments, although not predefined.

The mechanism of benefit is not clear, but our findings suggest that an abdominally placed cerclage may prevent the initiation of contractions. A previous study suggested that the higher the vaginal cervical cerclage is placed, the lower the risk of preterm birth (9) but this was in a more heterogeneous, lower risk population. In the very high-risk cohort of the present study, high vaginal cerclage was no better. The multiple and varied risk factors in the abdominal cerclage group suggests the treatment effect is unrelated to aetiology.

Severe complications were rare but those that did occur were in women with a vaginal procedure. Three of the four were related to cerclage failure, including trauma and sepsis. Multiple abdominal procedures associated with the abdominal cerclage may ultimately cause more longer-term morbidity and we were unable to evaluate this at this time. Further research should define longer-term morbidity including after the menopause, along with health economic evaluation of the procedure.

While further research is needed to confirm the value of TAC in other high-risk groups, our findings suggest it is likely to be beneficial to women with previous failed vaginal cerclage. Implications for practice include the need to increase the availability of transabdominal cerclage for suitable women, and the training of obstetricians in this uncommon practice. The

procedure is not technically difficult and most gynaecologists who undertake any form of pelvic surgery should be equipped with the fundamental skills.

Contributors

AS conceived the idea and is the guarantor. All the authors were involved in the design, collection, analysis, and interpretation of the data, the writing and critical review of the manuscript, and the decision to submit the manuscript for publication. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

This trial is registered with ISCRTRN Controlled Trials registry, ISCRTN89971375.

Disclaimer

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“Declaration of interests” (all authors)

None to declare.

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