OBSTETRICS

MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage

Andrew Shennan, MD; Manju Chandiramani, PhD; Phillip Bennett, PhD; Anna L. David, PhD; Joanna Girling, MA; Alexandra Ridout, MBBS; Paul T. Seed, PhD; Nigel Simpson, MBBS; Steven Thornton, PhD; Graham Tydeman, FRCOG; Siobhan Quenby, PhD; Jenny Carter, PhD

BACKGROUND: Vaginal cerclage (a suture around the cervix) commonly is placed in women with recurrent pregnancy loss. These women may experience late miscarriage or extreme preterm delivery, despite being treated with cerclage. Transabdominal cerclage has been advocated after failed cerclage, although its efficacy is unproved by randomized controlled trial.

OBJECTIVE: The objective of this study was to compare transabdominal cerclage or high vaginal cerclage with low vaginal cerclage in women with a history of failed cerclage. Our primary outcome was delivery at <32 completed weeks of pregnancy.

STUDY DESIGN: This was a multicenter randomized controlled trial. Women were assigned randomly (1:1:1) to receive transabdominal cerclage, high vaginal cerclage, or low vaginal cerclage either before conception or at <14 weeks of gestation.

RESULTS: The data for 111 of 139 women who were recruited and who conceived were analyzed: 39 had transabdominal cerclage; 39 had high vaginal cerclage, and 33 had low vaginal cerclage. Rates of preterm birth at <32 weeks of gestation were significantly lower in women who received transabdominal cerclage compared with low vaginal cerclage (8% [3/39] vs 33% [11/33]; relative risk, 0.23; 95% confidence interval, 0.07–0.76; *P*=.0157). The number needed to treat to prevent 1 preterm birth was 3.9 (95% confidence interval, 2.32–12.1). There was no difference in preterm birth rates between high and low vaginal cerclage (38% [15/39] vs 33% [11/33]; relative risk, 1.15; 95% confidence interval, 0.62–2.16; *P*=.81). No neonatal deaths occurred. In an exploratory analysis, women with transabdominal cerclage had fewer fetal losses compared with low vaginal cerclage (3% [1/39] vs 21% [7/33]; relative risk, 0.12; 95% confidence interval, 0.016–0.93; *P*=.02). The number needed to treat to prevent 1 fetal loss was 5.3 (95% confidence interval, 2.9–26).

CONCLUSION: Transabdominal cerclage is the treatment of choice for women with failed vaginal cerclage. It is superior to low vaginal cerclage in the reduction of risk of early preterm birth and fetal loss in women with previous failed vaginal cerclage. High vaginal cerclage does not confer this benefit. The numbers needed to treat are sufficiently low to justify transabdominal surgery and cesarean delivery required in this select cohort.

Key words: failed cerclage, late miscarriage, transabdominal cerclage, vaginal cerclage

Recurrent late miscarriage and early spontaneous preterm birth are 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 that probably represent genuine cervical incompetence or women who have traumatic cervical damage, such as that caused by surgery.[1] When evaluated by randomized controlled trial (RCT), vaginal cerclage has limited value, compared with conservative management (number needed to treat was 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 spontaneous preterm births are more likely to fall into that category.

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

We hypothesized that TAC would result in lower rates of late miscarriage and early preterm delivery compared with 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 to either stretch of the fetal membranes as the internal os opens[8] or loss of the cervical barrier to ascending infection.[7] A vaginal cerclage can also be placed higher in the cervix, by mobilizing the bladder (HVC). It is unknown whether this also results in lower rates of late miscarriage or preterm birth when compared with LVC.

Methods

Study design and participants

The Multicentre Abdominal vs Vaginal Randomised Intervention of Cerclage (MAVRIC) trial was a multicenter RCT funded by the J. P. Moulton Charitable Foundation and supported by the National Institute for Health Research Clinical Research Network. National Health Service Research Ethical Committee approval was obtained (REC 07/H1102/113), and the trial was registered on the International Standard Randomized Controlled Trial Registry (ISRCTN33404560).

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AJOG at a Glance

Why was this study conducted?

Vaginal cerclage is recommended in women with evidence of cervical insufficiency, such as a history of multiple recurrent mid trimester losses or early preterm birth. When vaginal cerclage fails, transabdominal cerclage has been advocated, with observational studies that suggest higher rates of success. We searched PubMed for original articles published in English before September 2018 with the search terms "preterm birth OR cerclage OR transabdominal cerclage OR high vaginal cerclage." There were no randomized studies that compared abdominal vs repeat vaginal cerclage.

Key findings

This randomized 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 a previous failed cerclage in the prevention of early preterm birth (<32 weeks of gestation) and fetal loss. High vaginal cerclage was no better than low vaginal cerclage in the prevention of early birth.

What does this add to what is known?

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

Women were eligible for trial inclusion if they had a history of spontaneous late miscarriage or preterm birth between 14 and 28 completed weeks of pregnancy with LVC in situ; however, rescue cerclage procedures (ie, cerclage inserted with exposed membranes) were excluded. Women were eligible for random assignment before conception or at <14 weeks of gestation. Only data from the first pregnancy after randomization was analyzed (figure 1).

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 years.

Procedures

Women with a previous failed cerclage were assigned randomly to TAC, HVC, or LVC. Techniques used were left to the local clinician's discretion. Details of surgical and anesthetic technique were collected (Table 1). All procedures were carried out by a consultant level surgeon (Table 2). Vaginal cerclage was inserted at <16 weeks of gestation with regional anesthetic and removed at 37 weeks of gestation, or earlier if preterm labor ensued. HVC involved mobilization of the bladder from the anterior cervix that allowed the suture to be placed higher and usually required regional anesthetic for removal. TAC was placed preconception or at <14 weeks of gestation as an open procedure under either regional or general anesthetic and required inpatient stay of up to 3 days. Women with TAC were scheduled for delivery by elective cesarean delivery at 38−39 weeks of gestation, with retention of the TAC for future pregnancies.

Randomization and masking

Women enrolled in MAVRIC were assigned randomly to TAC, HVC or LVC (1:1:1) with the use of a computer-generated randomization procedure that is incorporated in an internet-based secure trial database (www.medscinet.net/MAVRIC). Minimization was used to balance 2 prognostic variables: pregnancy at time of randomization and gestational age of previous late miscarriage or preterm delivery (Table 3). Because of the nature of the interventions, treatment allocation was known to both participants and healthcare professionals. Written informed consent was obtained from all participants, and baseline demographic characteristics, risk factors, and obstetric and gynecologic history were entered into the study-specific database.

Cerclage insertion was performed electively between 10 and 16 weeks of gestation (14 weeks for TAC) or before 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. Because HVCs and TACs are more specialist procedures, these were carried out in 1 of the designated centers to ensure that a suitably experienced surgeon completed the procedure. After cerclage insertion, women were monitored and treated according to the local clinicians' practice. All care was in line with contemporaneous evidence-based guidelines.

Outcomes

Our primary outcome on which the trial was powered was delivery at <32 completed weeks of pregnancy. Predefined secondary outcomes included neonatal death, serious operative complication rates, and complications of pre- and postconception cerclage (HVC and TAC).

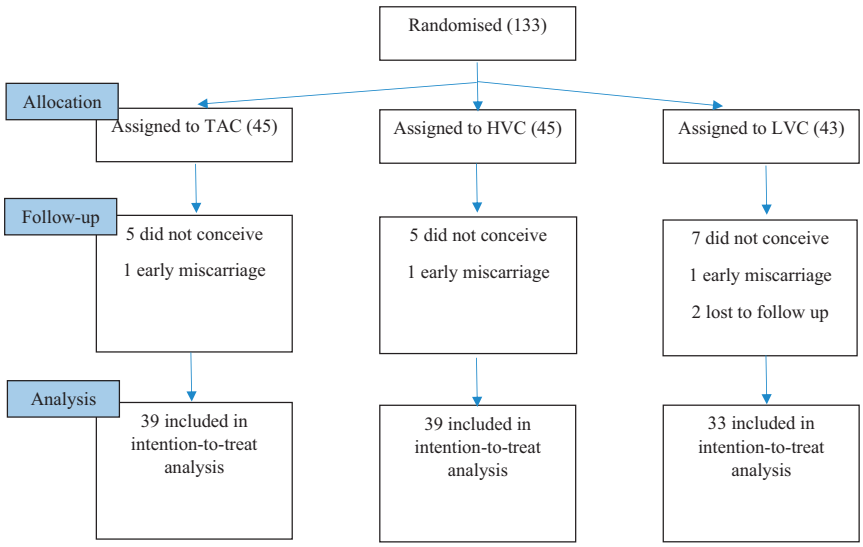
Pregnancy outcomes were obtained from case note review by trained research midwives. Women were considered to have had a spontaneous preterm birth if they had spontaneous onset of labor or experienced preterm rupture of membranes and delivered prematurely, regardless of mode of delivery. There were no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

Because there were no neonatal deaths, we performed an additional analysis by comparing 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

FIGURE 1
Treatment allocation and exclusions



Participant flow chart shows treatment allocation and exclusions.

HVC, high vaginal cerclage; *LVC*, low vaginal cerclage; *TAC*, transabdominal cerclage.

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Davis et al,[4] which was the best available evidence at the time. Our primary outcome was the rate of delivery at <32 complete weeks of gestation. Assuming a baseline event rate of 38% with LVC and 10% with TAC,[4] a total of 43 women in each of the 3 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 2 groups (effect of 28% absolute risk reduction). Given that this was a feasibility trial, we made no adjustments for multiple testing.

Statistical analysis

Statistical analyses were undertaken in Stata software (version 14.2; StataCorp 15.1, College Station, TX). Analysis was by modified intention to treat, with planned comparison of treatment effects for binary endpoints with the use of risk ratios and significance tests for both primary and secondary endpoints. The modification was to take into account patients who did not conceive after random assignment. A vaginal cerclage is unlikely to be considered in a nonpregnant patient; therefore, these women were removed to ensure that the analysis remained clinically valid. We also performed a per protocol analysis, although this was not predefined.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants

This was a multicenter RCT, with patients as the unit of randomization. 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).

TABLE 1
Details of surgical and anesthetic techniques

	Cerclage, n/N (%)					
	Transabdominal (n=39)		High vaginal (n=39)		Low vaginal (n=33)	
Procedure technique	Spontaneous preterm birth at <32/40 wks of gestation (n=3)	Delivery >32/40 wks of gestation (n=36)	Spontaneous preterm birth <32/40 wks of gestation (n=15)	Delivery >32/40 wks of gestation (n=24)	Spontaneous preterm birth <32/40 wks of gestation (n=11)	Delivery >32/40 wks of gestation (n=22)
Regional anesthesia	0/3	6/33 (18)	14/15 (93)	20/23 (87)	11/11 (100)	13/16 (81)
Mersiline tape[a]	1/3 (33)	4/28 (14)	12/13 (92)	21/22 (95)	9/10 (90)	16/17 (94)
≥2 Sutures inserted[b]	2/3 (66)	18/28 (64)	0/13	1/22 (5)	0/9	0/17
Cerclage tied anteriorly	0/3	4/28 (14)	13/13 (100)	20/21 (95)	10/10 (100)	12/15 (80)
Cerclage placed preconception	2/3 (66)	18/36 (50)	0/15	0/24	0/11	0/22
Subsequent rescue cerclage	0/3	0/36	3/15 (20)	1/24 (4)	2/11 (18)	0/22

[a] All other sutures were performed with monofilament suture material; [b] Inserted simultaneously at the time of procedure.

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TABLE 2
Operative details per randomization arm

Preterm birth at <32/40 wks of gestation	Cerclage		
	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)
Consultant grade surgeon, %	100	100	100
Surgeons, n	7	4	7
Blood loss, mL[a]	100 (50–150)	35 (20–60)	5 (5–20)
Operative time, min[a,b]	42 (30–50)	13.5 (10–15)	25 (20–32)
Rate of preterm birth at <32/40 wks of gestation, % (n/N)			
Overall	8 (3/39)	38 (15/39)	33 (11/39)
Primary surgeon	4 (1/25)	30 (10/33)	32 (8/25)
Other surgeons	15 (2/13)	60 (4/6)	50 (4/8)
Concurrent progesterone, % (n/N)	17 (6/36)	28 (10/36)	48 (14/29)
Rescue cerclage, % (n/N)	0 (0/39)	10 (4/39)	6 (2/33)

[a] Data are given as median (interquartile range); [b] Start of operation to completion

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One hundred thirty-nine participants were recruited and randomly allocated to a treatment. The first patient was recruited in January 2008. Recruitment ended in September 2014, when the planned recruitment target (n=129) had been exceeded. Seventy-nine women were not pregnant at the time of randomization, 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 2 participants who were known to have moved abroad.

The data monitoring committee was consulted in September 2018; there had been no further conceptions during the preceding 12 months, so the decision was made to proceed with analysis on 111 women. Only data from the next pregnancy after random assignment was analyzed (Figure 1).

Of the 111 participants who had conceived with known outcome, 39 participants were assigned randomly to TAC, 39 to HVC, and 33 to LVC. All first-trimester miscarriages (<13 weeks of gestation) after randomization were excluded from the analysis (3 excluded: 1 in the TAC, 1 in the HVC, and 1 in the LVC group). Almost one-half of TACs (49%, 19/39) were placed before conception; all of the HVC and LVC were placed at <16 weeks of gestation.

Baseline demographic characteristics are given in Table 4. The median gestation of failed cerclage was 22 weeks (interquartile range, 20–24). Our inclusion criteria defined cerclage failure as preterm delivery at <28 weeks of gestation; however, 69% of women (96/139) had a failed cerclage that resulted in late miscarriage (<24 weeks of gestation). 95% (105/111) of participants had ≥ 2 late-second trimester losses (97% of TAC, 95% of HVC, 91% of LVC). Most others had cervical shortening detected during screening for a previous preterm loss.

Patients were treated as per local clinical practice. Therefore 17% (6/36) of TAC, 28% (10/36) of HVC and 38% (14/29) LVC were prescribed progesterone. All women had a history of recurrent early delivery; the median number of late miscarriages was 2 (interquartile range, 1–5), and the median number of preterm births was 1 (interquartile range, 0–5).

TABLE 3
Variables used for minimization by trial allocation after exclusions

Variable	Cerclage, n (%)		
	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)
Pregnant at random assignment	20 (44.4)	16 (35.6)	15 (34.9)
Delivery at <24 wks of gestation in preceding pregnancy	31 (68.9)	26 (57.8)	29 (67.4)

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TABLE 4
Maternal baseline demographic characteristics

Treatment allocation	Cerclage			
	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)	All (N=111)
Age at time of consent, y[a]	31.9±5.1	32.1±5.3	31.8±5.1	32.3±5.4
Body mass index, kg/m^2[a]	29.9±6.9	30.1±7.0	29.9±6.9	30.1±7.0
Social class/occupation, 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, n (%)				
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	4 (4)

[a] Data are given as mean±standard deviation.

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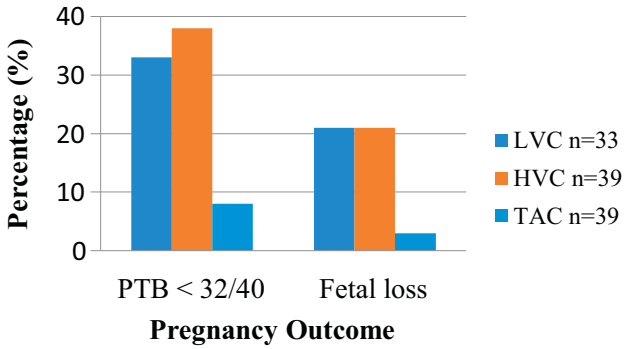
Outcomes

There was a statistically significant reduction in preterm birth at <32 completed weeks of gestational age (the primary outcome) in women who were allocated to TAC compared with LVC (8% [3/39] vs 33% [11/33]; relative risk 0.23, 95% confidence interval 0.07−0.76, *P*=.0157). There were no iatrogenic preterm deliveries among these women. The number needed to treat to prevent 1 spontaneous preterm birth was 3.9 (95% confidence interval, 2.32−12.1). There was no difference in rates of spontaneous preterm birth between HVC and LVC (38% [15/39] vs 33% [11/33]; relative risk, 1.15; 95% confidence interval, 0.62−2.16; *P*=.81). TAC also demonstrated benefit when compared with HVC (8% [3/39] vs 38% [15/39]; relative risk, 0.2; 95% confidence interval, 0.063−0.64; *P*=.0024). The number needed to treat was 3.2 (95% confidence interval, 2.0−7.4; Figure 2).

FIGURE 2
Pregnancy outcome by treatment allocation



Rates of primary outcome (delivery <32 completed weeks of pregnancy) and fetal loss (composite of late miscarriage and stillbirth) in each group.

HVC, high vaginal cerclage; *LVC*, low vaginal cerclage; *PTB*, preterm birth; *TAC*, transabdominal cerclage.

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No neonatal deaths occurred. Women with a TAC had fewer fetal losses (late miscarriage or stillbirth), compared with women with an LVC (3% [1/39] vs 21% [7/33]; relative risk, 0.12; 95% confidence interval, 0.016−0.93); *P*=.02). The number needed to treat to prevent 1 fetal loss was 5.3 (95% confidence interval, 2.9−26).

Serious adverse events (predefined as per protocol) were reported in 4 cases (2 cervical tears, 1 intensive therapy unit admission with sepsis, and 1 case of cardiomyopathy), all of which occurred in women with HVC (n=3) or LVC (n=1). Six women received a subsequent rescue cerclage (4 who were allocated to HVC; 2 who were allocated to LVC). The indication for rescue cerclage was painless dilation that was identified during routine preterm birth surveillance assessments (data available for only 3/6 women). Table 1 gives surgical and anesthetic details for each procedure divided by outcome; no specific trends are apparent, and techniques are spread equally across the outcome groups.

Seventy-two percent of women (28/39) with a TAC in situ delivered at term, compared with fewer than one-half of women with HVC (46%; 18/39) or LVC (48%; 16/33; Table 5).

TABLE 5
Pregnancy outcome by randomized allocation

	Cerclage, n (%)		
Treatment allocation	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)
Preterm, wks of gestation			
<32[a]	3 (8)	15 (38)	11 (33)
<34	4 (10)	18 (46)	13 (39)
<37	11 (28)	21 (54)	17 (52)
Live birth	38 (92)	31 (79)	26 (79)
Late miscarriage	1 (3)	7 (18)	7 (21)
Stillbirth	0	1 (3)	0
All fetal losses	1 (3)	8 (21)	7 (21)

[a] Primary outcome.
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Eight women did not receive treatment as per allocation (Table 6), because of patient choice after randomization or treatment allocation being judged inappropriate (for example, the cervix was found to be too short on vaginal examination at time of procedure). Results that are presented by intention to treat, however, were similar when analyzed as per protocol (Table 7).

Comment

Principal findings

This is the first RCT to compare TAC with VAC. Our findings show that TAC is superior to LVC in the prevention of early preterm birth for women with an unsuccessful previous vaginal cerclage pregnancy. Compared with LVC, there was no benefit of HVC. In addition, TAC was superior to LVC in the prevention of fetal loss (late miscarriage and stillbirth).

Clinical implications

Numbers needed to treat were modest to both prevent delivery at <32 weeks of gestation (<4 cases) and to prevent fetal loss (<6 cases); 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 and include the longer-term need for cesarean deliveries and associated morbidity.

Strengths and limitations

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

Women with a history of failed cerclage are rare. It is challenging to

TABLE 6
Details of patient crossovers from randomized allocation to treatment received

	Cerclage			
Identification no.	Randomization	Final procedure	Gestation[a]/detail	Outcome[a]
24	Low vaginal	Transabdominal	At 10+0/ patient preference	39+1
56	Low vaginal	Transabdominal	Preconception /patient choice	36+0
66	Low vaginal	High vaginal	At 14+0/patient preference	37+5
79	High vaginal	Transabdominal	At 12+5/patient preference	38+6
87	Transabdominal	Low vaginal	At 10+6/patient preference	38+0
88	Low vaginal	Transabdominal	At 10+2/no vaginal cervix on digital examination	37+6
111	Transabdominal	High vaginal	At 13+3/patient request	38+5
133	Low vaginal	High vaginal	At 13+0/transfer of care	38+2

[a] Weeks+days of gestation.
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TABLE 7
Primary outcomes by intention to treat and as per protocol analysis

Cerclage	Preterm birth <32 wks gestation						Fetal loss					
	Intention to treat analysis			As per protocol analysis			Intention to treat analysis			As per protocol analysis		
	Relative risk	95% Confidence interval	*P* value	Relative risk	95% Confidence interval	*P* value	Relative risk	95% Confidence interval	*P* value	Relative risk	95% Confidence interval	*P* value
Transabdominal vs low vaginal	0.23	0.07–0.76	.0078	0.21	0.65–0.70	.0059	0.12	0.016–0.93	.02	0.11	0.014–0.86	.018
Transabdominal vs high vaginal	0.2	0.063–0.64	.0024	0.19	0.058–0.59	.001	0.13	0.016–0.95	.029	0.12	0.015–0.88	.012
High vaginal vs low vaginal	1.15	0.62–2.16	.81	1.15	0.62–2.13	.80	0.97	0.39–2.38	1.00	0.96	0.39–2.36	1.00

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randomize such women into a trial in which there are strong previous beliefs about the perceived risk or benefit of the intervention, therefore lack of equipoise. This explains the length of time needed to reach the recruitment target, in spite of the national multicenter trial design. We found clinicians reluctant to randomize, 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 often have researched the treatment options extensively and have a fixed idea of which intervention would be best for them and are unwilling to be assigned randomly. We were unable to collect accurate screening data because of the referral nature of the trial.

The trial was underpowered to evaluate safety concerns, and meaningful subgroup analysis was not possible. Absolute numbers of women with previous cervical surgery, histories of urinary tract infections or bacterial vaginosis do differ slightly between arms; however, as per the CONSORT guidance, it is not recommended to carry out comparisons of randomized differences because these are likely to be the result of chance rather than bias and can be misleading.[9] Additionally, we were unable to analyze complications pre- and postconception with the abdominal procedure because of their rarity (none) and small numbers. No clinicians used laparoscopic TAC procedures; we therefore could not evaluate possible differences between this and other techniques, such as types of sutures. Other concerns that are related to abdominal cerclage include management of 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 performed safely up to 14 weeks of gestation, which leaves the abdominal cerclage in place.

Although the trial intended to evaluate rates of neonatal death, there were none. This suggests that women with a previous failed pregnancy at <28 weeks of gestation tend to have fetal losses at previable gestations in the second

TABLE 8
Cohort risk factors for spontaneous preterm birth by treatment allocation

Risk factor	Cerclage			
	Transabdominal (n=39)	High vaginal (n=39)	Low vaginal (n=33)	All (N=111)
Cervical surgery, n (%)	2 (5)	6 (15)	9 (27)	17 (15)
Late miscarriages, n[a]	2.12±1.15 (0–5)	1.70±1.12 (0–4)	1.97±1.08 (0–5)	1.99±1.15 (1–5)
Early delivery (late miscarriage/preterm birth at <28 wks of gestation), n[b]	2.73±1.12	2.65±1.03	2.91±1.27	2.76±1.13
≥2 Second trimester losses, n (%)	38 (97)	37 (95)	30 (91)	105 (95)
Congenital uterine anomaly, n (%)	3 (8)	4 (10)	3 (9)	10 (9)
Antiphospholipid syndrome (anticardiolipin or lupus anticoagulant), n (%)	1 (3)	2 (5)	0	3 (3)
Smoked during pregnancy, n (%)	3 (8)	1 (3)	4 (12)	8 (7)
Medical history, n (%)				
Recurrent urinary tract infections (>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	2 (6)	3 (3)
Domestic violence	0	0	0	0

[a] Data are given as mean±standard deviation (range); [b] Data are given as mean±standard deviation.

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trimester, if they recur. The mechanism of pregnancy failure that causes late miscarriage and early preterm birth (resulting in neonatal death) is likely to be the same; because we excluded early miscarriage, we believe our fetal loss rates are a meaningful comparator across treatments, although not predefined.

Comparison between TAC and HVC was not planned originally because we were investigating an improvement in preterm birth rates compared with standard practice, which at that time was LVC. Given the strong reduction in the rate of preterm birth in women with a TAC in situ and the similarity between the groups with HVC and LVC, it was considered appropriate to also compare TAC with HVC. TAC was shown to reduce preterm birth strongly at <32 weeks of gestation compared with HVC and LVC. These results remained highly significant, even after correction for multiple testing with the use of the Bonferroni correction (TAC vs LVC, P=.02; TAC vs HVC, P=.007).

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,[10] but this was in a more heterogeneous, lower risk population. In the very high-risk cohort of the present study, HVC was no better. The multiple and varied risk factors in the abdominal cerclage group suggests that the treatment effect is unrelated to cause (Table 8).

Research implications

Severe complications were rare; however, those that did occur were in women with a vaginal procedure. Three of the 4 were related to cerclage failure and included cervical trauma at early birth and sepsis. Multiple abdominal procedures that are associated with the abdominal cerclage ultimately may cause more long-term morbidity, and we were unable to evaluate this within this study. Future research should define long-term morbidity that is associated with the procedure (eg, pelvic pain, repeat surgery) alongside a health economic evaluation of the procedure and its outcomes over a woman's reproductive life and should include the reduced morbidity that is associated with fewer failed pregnancies.

Conclusion

Although further research is needed to confirm the value of TAC in other high-risk groups, our findings suggest that it is likely to be beneficial to women with previous failed vaginal cerclage. Implications for practice include the need to increase the availability of TAC for suitable women and the training of obstetricians in this uncommon practice. The procedure is not technically difficult, and most gynecologists who undertake any form of pelvic surgery should be equipped with the fundamental skills. ■

References

1. Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. Cochrane Database Syst Rev 2003;1:CD003253.

2. Owen J, Hankins G, Iams JD, et al. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. Am J Obstet Gynecol 2009;201:375.e1–8.

3. Dawood F, Farquharson R. Female Genital Tract Congenital Malformations. 2015;169-174. Available at: http://link.springer.com/10.1007/978-1-4471-5146-3. Accessed October 24, 2019.

4. Davis G, Berghella V, Talucci M, Wapner RJ. Patients with a prior failed transvaginal cerclage: a comparison of obstetric outcomes with either transabdominal or transvaginal cerclage. Am J Obstet Gynecol 2000;183:836–9.

5. Umstad MP, Quinn MA, Ades A. Transabdominal cervical cerclage. Aust N Z J Obstet Gynaecol 2010;50:460–4.

6. Debbs RH, DeLa Vega GA, Pearson S, Sehdev H, Marchiano D, Ludmir J. Transabdominal cerclage after comprehensive evaluation of women with previous unsuccessful transvaginal cerclage. Am J Obstet Gynecol 2007;197:317.e1–4.

7. Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1998;178:1035–40.

8. Mohan AR, Sooranna SR, Lindstrom TM, Johnson MR, Bennett PR. The effect of mechanical stretch on cyclooxygenase type 2 expression and activator protein-1 and nuclear factor-κB activity in human amnion cells. Endocrinology 2007;148:1850–7.

9. Bland JM, Altman DG. Comparisons within randomised groups can be very misleading. BMJ 2011;342:d561.

10. Cook JR, Chatfield S, Chandiramani M, et al. Cerclage position, cervical length and preterm delivery in women undergoing ultrasound indicated cervical cerclage: a retrospective cohort study. PLoS One 2017;12:e0178072.

Author and article information

From the Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London (Drs Shennan, Chandiramani, Ridout, and Carter and Mr Seed); the Parturition Research Group, Institute of Reproductive and Development Biology, Imperial College London (Dr Bennett); UCL EGA Institute for Women's Health, University College London (Dr David); and Barts and the London School of Medicine and Dentistry, Queen Mary University of London (Dr Thornton), London, UK; the Department of Obstetrics and Gynaecology, West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, Middlesex, UK (Dr Girling); the Department of Women's and Children's Health, University of Leeds, Leeds, UK (Dr Simpson); Forth Park Hospital, Fife Hayfield House, Kirkcaldy, UK (Dr Tydeman); and the Division of Biomedical Sciences, Warwick Medical School, University of Warwick, Coventry, UK (Dr Quenby).

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Corresponding author: Andrew Shennan, MD. Andrew.shennan@kcl.ac.uk