PROTOCOL TITLE:

MAVRIC: Multicentre abdominal versus vaginal randomised investigation of cerclage

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1. Background

Importance

Preterm birth (PTB) defined as birth before 37 weeks’ gestation, accounts for 6-10% of all births and is a major contributor to neonatal and infant morbidity and mortality.\(^1\) Spontaneous preterm birth (SPB) accounts for about three quarters of these births and births before 30 weeks of gestation accounts for most neonatal deaths.\(^2\) 90% of babies born before 33 completed weeks in the UK are transferred to the neonatal unit.\(^3\) Almost one-fifth of all infants born at less than 32 weeks gestation do not survive the first year of life.\(^4\) Few interventions have made an impact on morbidity and mortality of preterm babies; these are limited to the introduction of antenatal steroids\(^5\) and advances in neonatal intensive care.

Worryingly, the incidence of SPB continued to rise in the last decade, even in low risk women\(^6,\)\(^7\), confounded by the lack of effective preventative measures. In the United States in 2005, 12.5% (>500,000) of infants were born preterm, making the annual societal economic burden associated with PTB in excess of $26.2 billion.\(^8\) PTB also results in significant physical, emotional and psychological distress to the families involved. According to a recent editorial in the Lancet, research into PTB should be given priority, funded and undertaken without delay.\(^9\)

The cervix provides mechanical strength and prevents ascending infection from penetrating the intra-uterine space. Cervical insufficiency is defined as the inability of the uterine cervix to retain an intrauterine pregnancy to term, in the absence of contractions or labour, resulting in a second trimester loss or a PTB. Transvaginal cervical cerclage (TVC) is often the intervention of choice for a diagnosis of cervical insufficiency although it has a limited evidence base; only 1:25 TVCs are thought to be beneficial in current clinical practice.\(^10\) In some women with a history of cervical insufficiency, a PTB or a second trimester loss occurs despite having a cervical suture in situ. In these women, transabdominal cervical cerclage (TAC) may be an appropriate option. Placing the suture higher (close to the isthmus/ internal os) may improve its ability to maintain the mechanical barrier between the vagina and the intrauterine space.

Placement of the cervical suture transabdominally was first described in the 1960s by Benson and Durfee as an alternative in a small group of women in whom transvaginal placement was not possible.\(^11\) Novy went on to include previous failed TVC as an indication for transabdominal placement of the suture.\(^12\) Transabdominal procedures are performed with patients under a spinal or epidural block in the majority of cases. A Pfannenstiel incision is made and the suture is placed at the internal os. The uterine vessels are displaced laterally and the suture is guided through the broad ligament at the junction of the cervix and lower uterine segment by blunt perforation. The patients subsequently undergo scheduled caesarean section between 38 and 39 weeks and the cerclage is left in place for subsequent pregnancies.

Observational data of TAC in situations where TVC has failed suggests this approach is
highly successful with success rates often greater than 90%.\textsuperscript{13} A retrospective cohort series conducted by Davis et al.\textsuperscript{14} comparing TAC with a vaginal suture in early pregnancy in women with previous ‘failed’ vaginal sutures found that TAC is associated with a lower incidence of preterm delivery and preterm premature rupture of membranes (PPROM) in comparison with TVC. Preterm delivery at both <35 and <33 weeks’ gestation was less common in the TAC group (18% vs. 42%, p=0.04; 10% vs. 38%, p=0.01; respectively) than in the TVC group. A transvaginal cervicoisthmic cerclage (TVHC) as an alternative to TAC has been proposed.\textsuperscript{15} This study demonstrated that the transvaginal route could also be used to perform an efficient cervicoisthmic cerclage allowing the cerclage to be placed as high on the isthmus as with the abdominal route, but with the advantages of simplicity and rapidity of the vaginal route. Foetal survival following TVHC improved from 18% to 79% with no reported operative complications.

However, randomised controlled trials of cerclage have demonstrated that even high-risk women often have term pregnancies without intervention. TAC can be an expensive procedure requiring 2 laparotomies but if successful, can have substantial impact on outcome, in terms of gestation at delivery and a subsequent reduction in neonatal morbidity and mortality. We do not know if TAC is better than TVC in women with a failed TVC, nor do we know if high (TVHC) or low vaginal sutures result in better outcomes for a woman and her baby. Prospective randomised trials are needed to compare the effectiveness in terms of outcome and post-operative complications of TAC versus TVC, and TVHC versus TVC in women with a previous failed TVC.

High-risk women who are advised to have a TAC or TVHC in their subsequent pregnancy may have it done either pre-conceptionally or during early pregnancy. There is no evidence to suggest that a pre-conception cerclage may be more effective than one in early pregnancy, but has the advantage of not interfering with the uterine vasculature during pregnancy. In fact, in a case series of 19 women, preconception TAC was a safe alternative to TAC performed in pregnancy with no risk to the fetus and the authors suggest that it be considered in appropriate cases in women seen for pre-pregnancy counselling.\textsuperscript{16} In addition, insertion of the cerclage in pregnancy may be more difficult because of increased uterine dimensions, and complications of the procedures associated with either manipulating a gravid uterus. In an observational cohort study by Lotgering et al.\textsuperscript{17} where TVC was considered surgically unfeasible, there were few procedure-related major complications with TAC. In a cohort of 101 patients, in whom the procedure would be considered difficult, 3 women lost ≥500mls, 2 had rupture of membranes, 1 had exposure of membranes and 3 had painful micturition following the procedure. If TAC is inserted prior to conception, there is a theoretical risk of resultant sub-fertility.

The success of TAC or TVHC over TVC in this patient group may be due to the higher insertion of the suture at the level of the internal os. Unlike a TVC, a TVHC involves an incision in the vagina, mobilisation of the bladder and placement of the suture at the level of the internal os. The type of suture used and whether a “tail” is left varies. Similarly a TAC is more invasive as it requires two laparotomies. At caesarean section the baby is delivered by a transverse uterine incision above the level of the suture. Preterm labour or
miscarriage is a particularly difficult management issue regarding route of delivery, and may require hysterotomy or “Dilatation and Evacuation” through the suture. The suture is usually left in place for future pregnancies. Although TAC may be associated with a lower risk of perinatal death or delivery <24 weeks of gestation, it is also associated with a higher risk of operative complications.\textsuperscript{18} The major complication of TAC is bleeding at the time of insertion. Other complications include pregnancy loss and intrauterine growth restriction from inadvertent ligation of the uterine arteries.\textsuperscript{17} There is an urgent need to evaluate and compare complications of these different procedures.

Dual pathology has been found to be responsible in 5\% of women with a previous second trimester loss.\textsuperscript{18} One series (n=158) with a high risk of second trimester loss (25\%) found an incidence of 33\% for antiphospholipid antibodies.\textsuperscript{19} In a case series by Farquharson et al.\textsuperscript{20}, 40 cases are described where strict adherence to an investigation protocol and consistent treatment plan is implemented to explore transabdominal cerclage, the significance of dual pathology and increased preterm delivery. The presence of dual pathology, i.e. antiphospholipid syndrome or bacterial vaginosis, in conjunction with true cervical weakness, is associated with a 56\% risk of delivery before 34 weeks compared with 18\% for cervical weakness alone. The delivery rate at <24 weeks was 5\%. The manner by which placental pathology, antiphospholipid syndrome and previous cervical surgery influences outcome is not known and within this feasibility study, we will stratify for these potentially confounding factors.
2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

We hypothesise that either transabdominal (TAC) or high vaginal (TVHC) cervical cerclage may be associated with a lower risk of second trimester loss or preterm delivery at less than 32 weeks of gestation than transvaginal cervical cerclage (TVC).

We aim to compare:

1. the rate of delivery <32 weeks (on which the trial is powered)
2. the rate of neonatal death
3. serious operative complication rates
4. complications of pre and post conception sutures for TVHC and TAC

This feasibility trial will confirm and define the magnitude of benefit of TAC or TVHC compared to TVC, while determining the power required for a larger trial to demonstrate their safety and merit.
2.2 Trial Design

Study design
This is a multicentre randomised controlled trial of TAC or high transvaginal cervical cerclage (TVHC) versus TVC in high-risk women with a previous failed TVC sufficiently powered to determine if TAC results in better outcome, in terms of gestation at delivery and neonatal death. By also determining the likelihood of serious operative complications (blood loss, membrane rupture, miscarriage, stillbirth, intrauterine growth restriction) after TAC compared with TVC and the relevance of timing of TAC insertion (preconception vs. during early pregnancy) to outcome, we will be able to power future trials to assess the risk-benefit of such interventions.

Our control group will be women who receive a TVC in their index pregnancy. Women will be recruited from various centres across the country and referred to regional maternity units with established preterm delivery clinics / referral services if necessary. Often women who have had a failed vaginal cerclage, i.e. one that has resulted in a second trimester miscarriage or a preterm delivery at less than 28 weeks, will be seen for counselling following their early delivery as a matter of routine care. It will be at this point that they will be advised of the option to take part in the trial in a subsequent pregnancy. If a woman is eligible and she agrees to take part, she will be recruited and randomised to receive TAC or either a high or low TVC. If a woman presents when she is already pregnant (which will happen in the majority of cases), her eligibility will be ascertained and she will be recruited and randomised as appropriate.

Women will be recruited if they present pre-pregnancy or before they are 14 weeks’ pregnant. In the majority of cases, women will be referred and randomised in early pregnancy following an early pregnancy scan which confirms dating of the pregnancy, viability and no gross structural anomalies. Women will then be counselled regarding the trial and if they agree to take part, they will be consented. They will then undergo internet randomisation to receive a TVC, TVHC or a TAC. The procedures will be performed electively between 10 to 16 weeks of gestation, or for TVHC or TAC, pre-conceptually according to clinician preference. The TVC will be carried out at the woman’s own maternity hospital and the TAC or TVHC will be carried out at one of the designated centres by an operator skilled in the procedure. Trial management, including randomisation, will be via the internet.

The standard 'purse-string' vaginal cerclage will be similar to the stitch the woman has previously received. It is usually inserted under regional anaesthetic (an injection in the back) and she will usually be awake. She will usually go home the same day and will have the stitch removed at about 37 weeks' gestation, often without an anaesthetic, if labour and a vaginal delivery are planned. If she is due to have a caesarean section, the stitch may be removed at this time.

The high vaginal stitch (TVHC) takes longer to insert (because of the need to manipulate the bladder) but is similar to the standard vaginal stitch. As it involves mobilisation of
the bladder, there is a small risk of bladder injury and as it is more difficult to remove, it involves an anaesthetic for both insertion and removal. It can be put in preconceptually, and removed, if necessary, should a miscarriage occur. If a vaginal delivery is anticipated, the stitch may be removed at 37 weeks' gestation but if a caesarean section is planned, it may be left in situ and removed at the time of the section.

The abdominal stitch may be inserted pre-conceptually or before 16 weeks' gestation. Under a general anaesthetic, a laparotomy or laparoscopy is needed to insert the stitch. The procedure takes longer than either of the vaginal stitches and a woman may need to stay in hospital for up to 3 days, unlike the other two which allow her to be discharged on the same day. The chances of damage to the bladder or bowel may also be higher and the length of hospital stay longer than with the vaginal stitches. If the procedure is done preconceptually, a woman's fertility is not affected. She can try to get pregnant following her next period and will have routine antenatal care. An elective caesarean section will be booked at 38 to 39 weeks.

Following the insertion of the cerclage, women would be seen at regular intervals in clinics where they will be appropriately followed up and managed. If they need any further interventions such as antibiotics or antenatal corticosteroids, this will be given as per local hospital guidelines and as per their treating clinician’s practice, reflective of current evidence-based practice. If a woman receives a TVC or a TVHC, this will be removed at 37 weeks (unless a caesarean section is to be performed). If she was randomised to receive a TAC, an elective caesarean section will be booked at 38 - 39 weeks.

The timetable for the stages of the research is illustrated in Figure 1 (see attached).

**Ethics and Research Governance Compliance**

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996) and follow the principles of ICH-GCP. MHRA approval for the study was not required. The protocol is to be submitted for approval by a Research Ethics Committee (COREC) and the appropriated R&D committees. Written informed consent will be obtained and documented in the participant’s hand-held notes. A sticker will also be placed on the participant’s notes.

**Storage and use of cervical cerclages**

Removed cervical cerclages will be sent to the Maternal and Fetal Research Unit, St Thomas’ Hospital, until analysis. Samples will be measured and weighed and operator technique will be noted.
2.3 Trial Statistics

Eligible women are those with a previous failed TVC. They can present pre-pregnancy or at less than 14 weeks of gestation. In the majority of cases, women will be referred and randomised in early pregnancy following an early pregnancy ultrasound, which confirms a dating of the pregnancy and viability. Women who agree to take part will undergo internet randomisation to receive a TVC, TVHC or a TAC. The procedures will be performed electively between 10 and 16 weeks of gestation, or for a TVHC or a TAC, pre-conceptually according to clinician preference. The TVC will be carried out at one of the designated centres by an operator skilled in the procedure.

Power calculations, numbers of patients to be studied and data analysis

The trial is powered for the primary outcome of the rate of delivery at <32 completed weeks of gestation. As the study by Davis et al. is the best available evidence, we have powered this feasibility study on their outcome data where there was a preterm delivery rate of 38% with a TVC compared with 10% with a TAC. As a result, with 80% power at the 5% level of significance (2-tailed), we would need 43 women in each of the 3 groups: TVC, TVHC, and TAC to show a significant difference between TVC and each of the other groups. Although this is powered to detect a large relative risk reduction (absolute risk reduction of 28%), this is less then the literature suggests and we feel 80% power is therefore justified.

By undertaking this small feasibility study, we could power a larger trial to look at other important outcomes such as neonatal death and postoperative complications (blood loss, rupture of membranes, miscarriage, intrauterine growth restriction, bladder trauma, hospital admission and bed days), particularly between TVHC and TAC including pre and post conception.

Data will be entered on to an internet database as collected and transferred to the statistical package Stata (StataCorp, College Station, Texas) for analysis.

3 Trial Medication

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

i) ‘Purse-string’ transvaginal cervical cerclage (TVC)

ii) High transvaginal cervical cerclage (TVHC)

iii) Transabdominal cervical cerclage (TAC)
4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria
Previous miscarriage or preterm birth before 28 weeks’ gestation despite having a purse-string vaginal stitch in place.
Not yet pregnant or less than 14 weeks pregnant.

4.2 Exclusion Criteria
Inability or unwillingness to give informed consent.
Women under the age of 16.

4.3 Withdrawal of Subjects
In the event that a participant withdraws from the study (which may occur at anytime prior to cerclage insertion), she will continue to be seen as part of routine clinical care within the context of antenatal or prematurity clinics. She will only have procedures done which are clinically indicated.

Withdrawn subjects will be replaced in order to adhere to our power calculation for recruitment. The study team will retain data collected to the point of withdrawal for analysis and pregnancy outcome data will be obtained from maternity notes unless the participants specifically advise against its collection.

4.4 Concomitant Medication
Any medication or treatment that would form normal clinical management for these women at risk of preterm labour, i.e. antibiotics, progesterone, corticosteroids, tocolytics, etc. will be permitted according to local hospital guidelines and clinician preference.

4.5 Subject Compliance.
Concerns regarding compliance are not relevant in this study as the intervention is a surgical intervention.
5 Assessment of Safety

It is unlikely that the participants will be affected by a serious adverse event or a serious adverse reaction in this trial. The surgical interventions they will be receiving are those which would be offered routinely in clinical practice. Cervical cerclage insertion is an established surgical procedure, which is associated with minimal risks. These include infection, miscarriage, bleeding, difficulty with suture removal and preterm prelabour rupture of membranes. Transabdominal cerclage insertion is associated with a minimal risk of bladder and bowel damage. Other than the surgical intervention, these women will only receive those interventions which they would be receiving in routine clinical practice. Only unexpected serious adverse events / reactions which are unrelated to these clinical procedures will be reported as SAEs using the attached form. (Appendix 1)

5.1 Procedures for Recording and Reporting Adverse Events

Serious adverse Event (SAE), Serious Adverse Reaction (SAR)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;
Is life-threatening;
Required hospitalisation or prolongation of existing hospitalisation;
Results in persistent or significant disability or incapacity;
Is otherwise considered medically significant by the investigator.

Reporting Responsibilities

All SAE’s will be reported in the first instance to the chief investigator, Prof Andrew Shennan and discussed with the MAVRIC research team, unless the SAE is specified in this protocol as not requiring reporting. Subsequently, the sponsor and the main Research Ethics Committee will be notified as indicated on the COREC website (see Appendix 2). Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and will be reported in the normal way, on the appropriate CRF.

6. Direct Access to Source Data and Documents

Meetings will be held on a regular basis by the MAVRIC research team to monitor and audit the conduct of the research and review aspects of the study’s progress. The investigators and the institutions will permit trial-related monitoring, audits, REC review and regulatory inspections if appropriate by providing direct access to any collected data.
7 Ethics

The study will be conducted in line with the principles of the Declaration of Helsinki (1996) and the principles of ICH-GCP. The study protocol and other documentation has been submitted to the South East Research Ethics Committee for review. The address is: Kent and Medway Strategic Health Authority, Preston Hall, Aylesford, Kent. ME20 7NJ. Tel: 01622 271 3106. Any subsequent protocol amendments will be submitted to the REC for approval. The investigators will comply with ICH-GCP Guidelines over the reporting of adverse events and serious adverse events, as well as providing the REC with progress reports, and a copy of the Final Study Report.
References

THE MULTICENTRE RANDOMISED CONTROLLED TRIAL OF TRANSABDOMINAL VERSUS TRANSVAGINAL CERVICAL CERCLAGE.

Figure 1: Summary diagram of the MAVRIC study
Version 1. 10/08/07