


BMJ Open Emergency cerclage using double-level versus single-level suture in the management of cervical insufficiency (Cervical Occlusion double-level Stitch Application, COSA): study protocol for a multicentre, non-blinded, randomised controlled trial

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To cite: Kosińska Kaczyńska K, Rebizant B, Bednarek K, *et al*. Emergency cerclage using double-level versus single-level suture in the management of cervical insufficiency (Cervical Occlusion double-level Stitch Application, **COSA**): study protocol for a multicentre, non-blinded, randomised controlled trial. *BMJ Open* 2023;**13**:e071564. doi:10.1136/bmjopen-2023-071564

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-071564>).

Received 02 January 2023
Accepted 25 May 2023



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ABSTRACT

Introduction Cervical insufficiency accounts for 15% of recurrent pregnancy losses between 16 and 28 weeks of gestation. The aim of the study is to verify the effectiveness of emergency double-level cerclage with vaginal progesterone in cervical insufficiency treatment in terms of the prevention of preterm delivery before 34 weeks of gestation.

Methods and analysis This trial is a multicentre, non-blinded, randomised study with 1:1 allocation ratio. The study is conducted at tertiary perinatal care departments in Poland. It will include patients with cervical insufficiency with the fetal membranes visible in the open cervical canal or protruding into the vagina between 16+0 and 23+6 weeks of pregnancy. They will be randomised into two arms: emergency single-level cerclage with vaginal progesterone or double-level cerclage with vaginal progesterone. All will be administered antibiotics and indomethacin. The primary outcome is the rate of deliveries below 34+0 weeks of gestation, while secondary outcomes include gestational age at delivery, neonatal outcomes, maternal outcomes according to the Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth and cerclage procedure complications. The planned number of participants according to the power analysis is 78.

Ethics and dissemination The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement. It was created according to the requirements of the Declaration of Helsinki for Medical Research involving Human Subject. Ethical approval was obtained from the Ethics Committee of the Centre of Postgraduate Medical Education (no. 1/2022). The study protocol was approved and published by ClinicalTrials.gov (posted on 24 February

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The prospective multicentre randomised protocol using rigorous methods and outcomes according to the Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth to investigate the effectiveness of double-level emergency cerclage with vaginal progesterone.
- ⇒ The homogeneous study group treated according to the strict protocol with unequivocal definitions.
- ⇒ The study outcomes, which are the rate of deliveries below 34+0 weeks of gestation and neonatal mortality and morbidity, are the crucial points in perinatal care.
- ⇒ The main limitation of the study is that it may not be blinded.

2022). All participants gave a written informed consent. After completion of the study its results will be published in a peer-reviewed English language journal.

Trial registration NCT05268640.

INTRODUCTION

Context

Cervical insufficiency is characterised by the occurrence of painless dilatation of the cervix during the second or early third trimester of pregnancy. As a result of shortening and opening of the cervix, despite the lack of recognisable uterine contractions, the fetal membranes protrude into the cervical canal and then into the vagina, which results in preterm premature rupture of membranes

and miscarriage or preterm delivery. The condition occurs in approximately 0.1% of women.¹ It accounts for 15% of recurrent pregnancy losses between 16 and 28 weeks of gestation.¹

Current knowledge

In case of cervical insufficiency, when the fetal membranes are visible in the open external cervical os or protrude into the vagina, emergency cervical cerclage may prolong the pregnancy. Observational studies showed an extension of pregnancy duration by 4–9 weeks after emergency cerclage insertion compared with bed rest alone.^{2–5} Therefore, it is a procedure recommended by gynaecological societies around the world.^{6–8} The efficacy of the emergency cerclage was investigated in a single prospective randomised trial involving 23 women. The study revealed that emergency cerclage significantly extended the duration of pregnancy compared with bed rest alone (54 days vs 20 days, $p=0.046$). The rate of preterm deliveries before 34 weeks of gestation was significantly lower in the cerclage group (53.8% vs 100%, $p=0.02$). No significant difference was found in neonatal survival rates, while compound neonatal morbidity was significantly lower in the cerclage group (62.5% vs 100%, $p=0.02$).⁴ Currently there is an ongoing randomised controlled, multicentre trial aimed to determine if an emergency cervical cerclage reduces pregnancy loss in women who present with cervical dilatation and exposed unruptured, fetal membranes between 16+0 and 27+6 weeks.⁹ However, even after cerclage placement a large number of women deliver before 34 weeks of gestation. Therefore, novel tools or operational techniques are required for longer maintenance of pregnancy and more effective reduction in the percentage of deliveries before 34 weeks of gestation.

To date, no prospective randomised trial evaluating the efficacy of emergency double-level cervical cerclage has been published. Double stitch in cervical insufficiency was evaluated in four studies. Three of them analysed the effectiveness of a double-level stitch in history-indicated or ultrasound-indicated cerclages and found no significant reduction in the rate of preterm deliveries.^{10–12} The recently published study by Xu *et al* is the first one investigating the usefulness of a double-level emergency cerclage. The authors conducted a retrospective analysis of a single and double-level emergency cerclage before 26 weeks of gestation. They found women with double-level cerclage to deliver significantly later (32.71 ± 5.54 weeks vs 27.99 ± 4.70 weeks, $p=0.028$). In their study a significant decrease in the incidence of spontaneous preterm birth at less than 34 weeks and less than 32 weeks in the two-stitches group was observed ($p=0.034$; $p=0.013$, respectively). The neonatal intensive care unit admissions rate were significantly reduced as well ($p=0.035$).¹³

Research hypothesis and study aims

On the basis of assumption that emergency cerclage improves perinatal outcome, this research hypothesis assumes that placing emergency double-level cerclage

with vaginal progesterone treatment will significantly extend the duration of pregnancy and reduce the rate of deliveries before 34 weeks of gestation in case of cervical insufficiency with visible fetal membranes in comparison to a single-level cerclage with vaginal progesterone, therefore decreasing neonatal mortality and morbidity. Double-level cerclage will be characterised by greater resistance to cervical opening, less common tearing through the cervix, and a more effective reconstruction of the closed part of the cervical canal. It is possible that placing two sutures at two levels may induce the process of scarring in the cervix, which may also decelerate the opening of the cervix. The reconstruction of the closed part of the canal may offer the possibility of reconstructing the mucus plug in the canal. The mucus plug serves as a protection against the entry of infectious agents from the vaginal side, both in the mechanical and immunological mechanisms. It contains neutrophils, granulocytes and macrophages, lactoferrin, calprotectin, defensins and secretory inhibitors of leucocyte proteinases with antibacterial, antiviral and antifungal activity.¹⁴ Its presence and function are crucial for the maintenance of pregnancy. Vaginal progesterone, administered both in the double-level and in the single-level cerclage groups, may also play a role in the maintenance of the cervical mucus plug. In case of the application of history-indicated cerclage, the procedure is usually performed at 12–14 weeks of gestation. Therefore, the stitches are performed on a firm and long cervix containing normal cervical mucus. We hypothesise that this is the reason why no differences in its effectiveness were observed in previously published studies on women with history-indicated cerclages. Our study is the first prospective one investigating the effectiveness of single-level or double-level cerclage with vaginal progesterone therapy in women with membranes protruding through the open cervix into the vagina, therefore with no closed cervical canal and no cervical mucus.

As no prospective studies on single-level and double-level emergency cerclage has been published up till now, investigating it in a randomised controlled trial will fill the gap and provide credible scientific evidence, which can be used in future recommendations for cervical insufficiency management.

The aim of the study is to verify the effectiveness of emergency double-level cerclage with vaginal progesterone therapy in cervical insufficiency with visible membranes in terms of the prevention of preterm delivery before 34 weeks of gestation and improving perinatal outcome.

METHODS AND ANALYSIS

Study setting

COSA (Cervical Occlusion double-level Stitch Application) trial is a multicentre, non-blinded, randomised study with a nested qualitative evaluation and 1:1 allocation ratio. The study was started in March 2022 and is currently conducted at seven tertiary perinatal care departments in Poland. The Department of Obstetrics, Perinatology

and Neonatology, Centre of Postgraduate Medical Education in Warsaw is the main research centre. There are six co-operative centres: 1st Department of Obstetrics and Gynecology, Centre of Postgraduate Medical Education in Warsaw, Department of Obstetrics and Gynecology, Pomeranian Medical University in Szczecin, Department of Perinatology, Obstetrics and Gynecology, Polish Mother's Memorial Hospital—Research Institute in Łódź, Department of Obstetrics and Gynecology, Oncological Gynecology and Gynecological Endocrinology, Medical University of Gdansk, 1st Department of Obstetrics and Gynecology, Medical University of Warsaw and Department of Obstetrics, Women's Diseases and Oncological Gynecology, Nicolaus Copernicus University. The trial is recruiting other research centres willing to participate. The planned completion of the study will be in February 2025.

Eligibility criteria

Women hospitalised due to cervical insufficiency with cervical dilatation with visible fetal membranes in the external os or the protrusion of the fetal membranes into the vagina before 24 weeks of pregnancy will be recruited to the study.

The inclusion criteria comprise: maternal age 18 years or older, single pregnancy, gestation age 16+0 weeks to 23+6 weeks, viable fetus, physical examination of the fetal membranes visible in a dilated external cervix, informed consent given by women.

Exclusion criteria comprise any of the following occurring before the administration of the cerclage: preterm premature rupture of membranes, vaginal bleeding, active uterine contractions, fetal demise, fever, intrauterine infection, genetic defects of the fetus, lethal fetal malformations, congenital uterine defects, multiple pregnancy. Intrauterine infection will be diagnosed if maternal fever (defined by a body temperature $\geq 38^{\circ}\text{C}$) with no alternative cause identified and at least two symptoms among the following appear: fetal tachycardia >160 bpm for 10 min or longer, uterine pain, purulent vaginal discharge, white blood cell count $>15 \times 10^9/\text{L}$ in the absence of corticosteroid treatment or increased plasma C-reactive protein >10 mg/L.

All women diagnosed with cervical insufficiency, who meet the inclusion criteria and do not meet the exclusion criteria, will be invited to participate in the study. Recruitment began on 11 March 2022. After a profound explanation of the study and handing information leaflets, women will be offered a written consent in two copies—one for the participant, and one for storage at the study site. Those not willing to participate will be provided with antenatal care according to the standard protocol. It includes single-level cerclage, progesterone and perioperative antibiotic treatment (ampicillin or cefazolin depending on the recruitment centre). Patients, who will agree to participate in the study, will be randomised into two subgroups—single-level and double-level cervical

cerclage arm. All participants will be covered by third-party insurance (Wiener, policy no. COR254937).

Allocation and implementation

Randomisation was performed using a web-based Sealed Envelope system by the main researcher (KKK). The system randomly assigned subsequent numbers into two arms with a 1:1 allocation ratio. Ninety records (from 1 to 90) were randomised into two subgroups (single-level and double-level cerclage arm) and will be assigned to individual participants in the order they will be diagnosed and recruited at any of the research centres. Therefore the patients will be numbered in order of recruitment, irrespective of the site at which they were recruited. As it is a non-blinded trial, the assignment to single-level or double-level cerclage arm will be revealed to both the participants and researchers. Blinding is not possible due to the nature of the study. Researchers from any of the research centres participating in the study will enrol patients at their own centre and assign them with specific subsequent numbers. At this moment the participants' medical data will be anonymised. After the recruitment, the anonymised medical data of the participant will be sent to the main research centre (Department of Obstetrics, Perinatology and Neonatology, Centre of Postgraduate Medical Education in Warsaw). The personal data of the participants will be available only to the researchers from the centre where the participant was recruited.

Intervention

The study flow chart is shown in figure 1. Each patient will undergo a swab of cervico-vaginal discharge for aerobic and anaerobic bacteria and fungi, as well as for *Mycoplasma*, *Chlamydia* and *Ureaplasma* on admission to the hospital (three samples collected at the same time). Each patient will be administered progesterone vaginally 100 mg two times a day from the diagnosis of cervical insufficiency (if it was not administered earlier) until 34+0 weeks of gestation. On admission, empirical antibiotic therapy will be administered. It includes ceftriaxone 2.0 g intravenously one time a day, clarithromycin 500 mg orally two times a day and metronidazole 500 mg intravenously three times a day for 7 days.¹⁵ If any specific pathogens are detected in the cervical culture the antibiotic therapy will be modified according to the antibiogram. After 23+0 weeks of pregnancy, pregnant women will receive a course of corticosteroid therapy (betamethasone, two doses of 12 mg intramuscularly, 24 hours apart) if the risk of delivery within 7 days will be assessed as high. However, the decision on the corticosteroids administration will be made by a clinician after considering individual patient's risks. The cerclage will be applied within 48 hours after admission to the hospital. Perioperative indomethacin will also be administered for 48 hours in order to reduce the inflammatory reaction and for tocolytic effect (75 mg two times a day for 48 hours starting on the day of cerclage placement).¹⁶

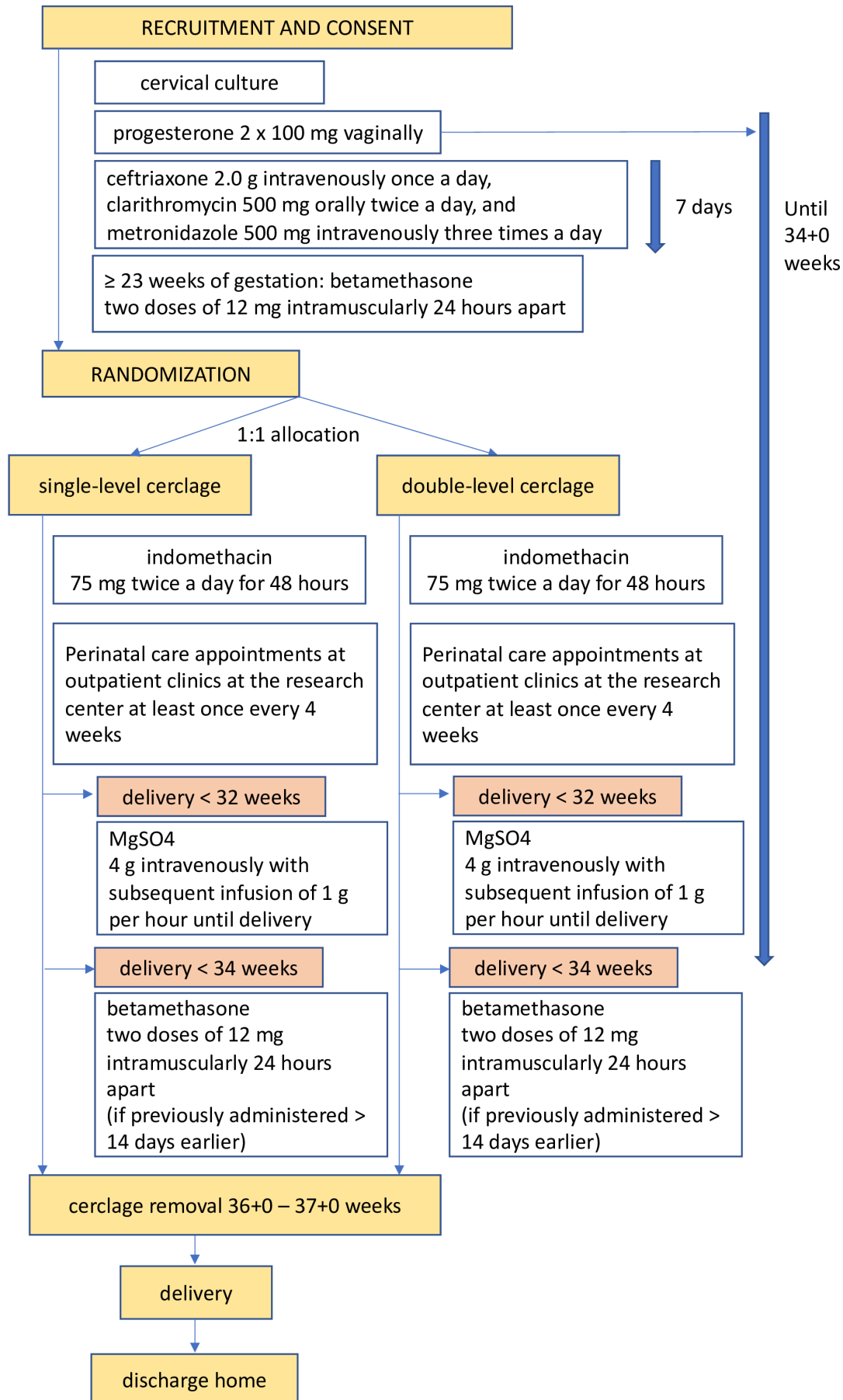


Figure 1 Study flow chart. MgSO₄ -magnesium sulfate.

Participants allocated to a single-level cerclage arm will have McDonald cerclage performed by an obstetrician or perinatologist. It is the standard management of cervical insufficiency. A circular suture will be placed around the cervix in the operating theatre under regional anaesthesia, after vaginal disinfection and visualisation of the cervix.¹⁷ If the fetal membranes protrude into the vagina, patients will be placed in the Trendelenburg position. Additional filling of the urinary bladder with saline and/or amnioreduction may be performed to gain withdrawal of the membranes into the cervical canal. Synthetic surgical sutures, braided, made of polyethylene terephthalate, coated with silicone (Yavo PE 2 USP, RS129PE) will be used for the cerclage.

If the patient is allocated to a double-level cerclage arm, two separate cervical sutures will be applied. The first suture will be performed analogously as the one in the McDonald's technique. It will be tied up and then, while pulling the cervix down, the second cerclage will be placed around 1 cm above the first one. The same Yavo PE 2 (RS129PE) suture will be used for both cerclages.

Analgesics will be administered after the procedure depending on the patient's needs (paracetamol up to 4.0 g per day).

The participants will be hospitalised for at least 48 hours after cerclage placement. After 48 hours, one of the obstetricians/perinatologists will decide if discharge home is possible.

All participants will be followed-up until delivery. They will be offered standard perinatal care in the outpatient clinics at the department that recruited them to the study. Antenatal appointments will be arranged according to the patients' needs, at least once every 4 weeks. In the absence of any other indications for delivery, cerclage will be removed at 36+0 to 37+0 weeks of gestation in both study arms.

In case of imminent delivery before 34+0 weeks, a single course of corticosteroid therapy (betamethasone, two doses of 12 mg intramuscularly, 24 hours apart) will be repeated if corticosteroids were administered more than 14 days earlier.

In case of delivery before 32+0 weeks magnesium sulfate will be administered for fetal neuroprotection (4 g intravenously within 20 min with a subsequent intravenous infusion of 1 g per hour until delivery).

The study will be discontinued if significantly more cases of fetal demise, miscarriages or preterm deliveries before 34 weeks of gestation will be observed after the recruitment of 39 participants (50%) in double-level cerclage arm. Protocol amendments will be communicated to the ClinicalTrials.gov registry and Ethics Committee of the Centre of Postgraduate Medical Education.

This is a per-protocol analysis randomised control trial. The final analysis will include only patients who had the treatment originally allocated.

Outcomes

The primary outcome is:

- ▶ Number and rate of deliveries below 34+0 weeks of gestation.

The secondary outcomes are:

- ▶ Gestational age at delivery (in weeks).
- ▶ Time from cerclage administration to delivery (in days).
- ▶ Fetal demise.
- ▶ Neonatal outcomes (number of cases and rates):
 - Birth weight (in grams).
 - Fifth-minute Apgar score.
 - Congenital infections.
 - Respiratory morbidity (breathing disorders requiring oxygen therapy, non-invasive or mechanical ventilation, respiratory distress syndrome defined as the need of surfactant and ventilation as a result of prematurity).
 - Hospitalisations in the neonatal intensive care unit.
 - Early neurodevelopmental morbidity (intraventricular haemorrhage, hypoxic-ischaemic encephalopathy, periventricular leukomalacia).
 - Gastrointestinal morbidity (necrotising enterocolitis).
 - Retinopathy of prematurity (requiring laser or ranibizumab administration).
 - Newborn's death before the discharge home.
- ▶ Cerclage procedure complications occurring within 48 hours after cerclage placement (number of cases and rates):
 - Excessive vaginal bleeding causing haemoglobin concentration drop by 1 g/dL.
 - Intrauterine infection diagnosed if maternal fever (defined by the body temperature $\geq 38^{\circ}\text{C}$) with no alternative cause identified and at least two symptoms among the following appear: fetal tachycardia >160 bpm for 10 min or longer, uterine pain, purulent vaginal discharge, white blood cell count $>15 \times 10^9/\text{L}$ in the absence of corticosteroid treatment or increased plasma C-reactive protein >10 mg/L).
 - Prelabour rupture of membranes.
- ▶ Maternal outcomes (number of cases and rates):
 - Maternal mortality.
 - Miscarriage.
 - Intrauterine infection diagnosed if maternal fever (defined by the body temperature $\geq 38^{\circ}\text{C}$) with no alternative cause identified and at least two symptoms among the following appear: fetal tachycardia >160 bpm for 10 min or longer, uterine pain, purulent vaginal discharge, white blood cell count $>15 \times 10^9/\text{L}$ in the absence of corticosteroid treatment or increased plasma C-reactive protein >10 mg/L) between 48 hours after cerclage and delivery.
 - Prelabour rupture of membranes.
 - Cervical laceration after cerclage placement.

The outcomes were developed according to the Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth.¹⁸ The course of pregnancy (miscarriage, gestational hypertension, pre-eclampsia, cholestasis of pregnancy, gestational diabetes mellitus) and delivery



(spontaneous or induced, caesarean or vaginal) will be analysed. The study protocol will take into account variables such as age, body mass index (BMI), obstetrical history, microbiological tests of cervicovaginal fluid, etc. Each of them may have an impact on the endpoints of the study. Several smaller models will be analysed from this main one, and each is nested inside the main model, for example, age or BMI and results of microbiological tests.

Adverse events

Cerclage procedure complications occurring within 48 hours included in the secondary outcomes will be reported by the researchers. Other assessed and reported adverse events will include:

- ▶ Preterm rupture of membranes after 48 hours following cerclage placement.
- ▶ Vaginal bleeding after 48 hours following cerclage placement.
- ▶ Visible cervical lacerations.
- ▶ Fetal demise after cerclage application.
- ▶ Cerclage tearing through the cervix.

Sample size

The only published randomised trial evaluating the effectiveness of emergency cerclage in comparison with conservative management and bed rest showed that the rate of deliveries before 34 weeks of gestation was 53%.⁴ A total sample size of 78 women will provide 90% power to detect a reduction in preterm deliveries before 34 weeks from 53% to 29% in women in whom double-level cerclage was applied (two-sided $\alpha=0.05$). Assuming 10% of women excluded or lost to follow-up it will be necessary to approach 86 patients diagnosed with cervical insufficiency.

Xu *et al* performed a retrospective comparison of a single-level and double-level emergency cerclage. According to their results 92.3% of women with single-level cerclage and 46.2% of women with double-level cerclage delivered before 34 weeks of gestation.¹³ A total sample size of 48 women would provide 90% power to detect a reduction in preterm deliveries before 34 weeks from 92% to 46% in women in whom double-level cerclage was applied (two-sided $\alpha=0.05$). To minimise the bias and risk of not receiving significant results we decided to include 86 women to the study.

Statistical methods

Variables will be described as medians, IQRs or numbers and percentages. The Mann-Whitney test and the Fisher's exact test will be used for statistical analysis. Kaplan-Meier curves will be used to visualise the time courses of pregnancies after intervention. Potential associations with the prolongation >34 weeks of gestation will be analysed using a logistic regression analysis and reported as ORs and 95% CIs. P values of <0.05 will be considered significant and all tests will be two-tailed. Data will be analysed using Statistica V.13.1.

Patient involvement

Patients were involved in the design of the information leaflet of the study. After initial preparation of the text it was given to randomly chosen patients and revised after discussion with them to make it easy to understand. Patients were not involved in other stages of the study design or conduct. When the study results will be published, the participants will be informed of the results by a study newsletter suitable for a non-specialist audience.

Study's strengths and limitations

This is the study investigating the double-level emergency cerclage with vaginal progesterone therapy. It is a prospective randomised trial conducted at many tertiary perinatal centres in Poland. The study will introduce information on the management of cervical insufficiency with membranes visible through the cervical os. The protocol is rigorous and strict with unequivocal definitions. The study outcomes, which are the rate of deliveries below 34+0 weeks of gestation and neonatal mortality and morbidity, are the crucial points in perinatal care. The main limitation of the study is that it may not be blinded. The obstetrician/perinatologist performing cerclage must know what kind of cerclage to perform. Any of the physicians examining the patient can verify how many sutures were applied during examination. The participants cannot be blinded as well, because in case of emergency they may be admitted at any other hospital except for the research centres and in case of delivery, the removal of only one suture when two were placed may be harmful for the cervix and cause its amputation. Therefore, both the researchers and participants will be notified of which arm of the procedure technique the participant was assigned to. The other limitation is that the study protocol was developed to investigate the rate of deliveries below 34 weeks of gestation as a primary outcome. The sample size was calculated in order to gain significant results. However neonatal mortality and morbidity, which are crucial in terms of perinatal outcomes. The study is underpowered for the most important clinical outcome—fetal/neonatal loss. However, maternal and neonatal outcomes are reported as secondary outcomes of the study.

ETHICS AND DISSEMINATION

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement. It was created according to the requirements of the Declaration of Helsinki for Medical Research involving Human Subject. Ethical approval was obtained from the Ethics Committee of the Centre of Postgraduate Medical Education (no. 1/2022). The study protocol was approved and published by ClinicalTrials.gov (posted on 24 February 2022). All participants gave a written informed consent.

Data on pregnancy, delivery and neonatal outcomes will be collected from the research centre maternity and neonatal records by researchers from this centre. The data will be anonymised and coded according to the randomisation number. The data will be entered by one of the researchers, double checked by another and then transferred to the main research centre. If a participant delivers at any other hospital, the same data will be collected during a telephone interview by one of the researchers after delivery. Encoded data will be stored at the main research centre (Department of Obstetrics, Perinatology and Neonatology, Centre of Postgraduate Medical Education in Warsaw) for 5 years after the completion of the trial and protected by the data protection officer (email: iod@cmkmp.edu.pl; phone: +48 22 5601004). After entering the data to the database at the main research centre, they will be available for all the researchers. A data monitoring committee, consisting of two experts external to the study, will assess the study progress, safety data and adverse events.

After completion of the study its results will be published in a peer-reviewed English language journal.

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Contributors The trial management group comprises KKK, BR, KB, AK, KM-P, DF-T, PU, SK, AT, MG, PK, MŻ and RB-B-S, all of whom contributed to the writing and editing of the protocol. KKK performed the randomisation. KKK invented the study hypothesis. KKK, BR, KB, AK, KM-P, DF-T, PU and SK wrote the protocol, while AT, MG, PK, MŻ, FAD and RB-B-S edited the final version. All authors read and approved the final manuscript. These will also be the authors for the publications reporting the results of the study.

Funding The trial was funded by the Centre of Postgraduate Medical Education, Warsaw, Poland. Grant number 501-1-022-26-21 (third party liability insurance only). Centre of Postgraduate Medical Education will not influence the design of the study and the collection, analysis, interpretation of data or writing of the manuscript in any way.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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