
**STUDY PROTOCOL**

# Cervical Pessary for Prevention of Spontaneous Preterm Birth in Singleton Pregnancies without prior preterm birth and with short cervix: a randomized controlled trial

**Abbreviation:** TVU, transvaginal ultrasound; CL, cervical length; PTB, preterm birth; SPTB, spontaneous preterm birth; OR, odds ratio; CI, confidence interval; GA, gestational age; RCT, randomized controlled trials; GCP, Good Clinical Practice; SD, standard deviation

## SUMMARY

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| **Title** | Cervical Pessary for Prevention of Spontaneous Preterm Birth in Singleton Pregnancies without prior preterm birth and with short cervix: a randomized controlled trial. |
| **Study location** | University of Naples Federico II |
| **Objective** | To test the hypothesis that in asymptomatic singleton pregnancies without prior SPTB but with short TVU CL the insertion of a cervical pessary would reduce the rate of SPTB <34 weeks |
| **Study design** | Single center prospective randomized trial |
| **Study population** | Asymptomatic singleton gestations without prior SPTB and with TVU CL ≤25mm |
| **Exclusion criteria** | - Multiple gestations<br>- Prior SPTB<br>- Rupture membranes, cerclage or pessary, or vaginal bleeding at the time of randomization<br>- Major fetatl abnormalities<br>- Chromosomal abnormalities |

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| **GA at randomization** | 18 0/7 – 23 6/7 |
| **Duration of study period** | 2 years (1 year enrollment + 1 year data analysis) |
| **Estimated study period for enrollment** | October 2016 – October 2017 |
| **Estimated sample size** | 300 singleton pregnancies |
| **Primary outcome** | SPTB <34 weeks |

## INTRODUCTION

Preterm birth (PTB) is a major cause of perinatal morbidity and mortality. Worldwide, about 15 million babies are born too soon every year, causing 1.1 million deaths, as well as short- and long-term disability in countless survivors.

Different strategies have been studied for prevention of spontaneous PTB (SPTB) in randomized controlled trials (RCTs), including progesterone, cerclage, cervical pessary, as well as lifestyle modification, such as smoking cessation, diet, aerobic exercise, and nutritional supplements. Most successful effort to reduce the incidence of SPTB have focused on women with risk factors, such as prior SPTB. However, most SPTB occur in women who have no such history. The evidence supports the use of vaginal progesterone in singleton gestations without prior SPTB but with short transvaginal ultrasound (TVU) cervical length (CL). Based on this evidence, universal TVU CL has been proposed for all singleton gestations without prior SPTB as a screening method for SPTB.

The cervical pessary is a silicone device that has been used to prevent SPTB. The leading hypotheses for its mechanisms are two: that the pessary helps to keep the cervix closed, and that the pessary changes the inclination of the cervical canal so that the pregnancy weight is not directly above the internal os.

## STUDY OBJECTIVES

Thus, we aim to test the hypothesis that in asymptomatic singleton pregnancies without prior SPTB but with short TVU CL the insertion of a cervical pessary would reduce the rate of SPTB <34 weeks.

## METHODS

## STUDY DESIGN

The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

This will be a prospective, single center randomized trial of asymptomatic singleton pregnancies without prior SPTB but with short TVU CL who will be randomized to either pessary (i.e. intervention group) or no pessary (i.e. control group) at Division of High Risk Pregnancy, Departement of Obstetrics and Gynecology, University of Naples Federico II (Napoli, Italy)

## INCLUSION AND EXCLUSION CRITERIA

Eligible women will be those referred to our Insitution due to a diagnosis of short cervix during the routine anatomy scan. In our Division, the measurement of the cervix by using TVU will be repeat and those found to have TVU CL ≤25mm will be approached by the research staff and consented. An information leaflet concerning the study will be given to the women.

*Inclusion criteria are:*

- Singleton gestations
- No prior SPTB
- 18-50 years of age
- TVU CL ≤25mm

*Exclusion criteria are:*

- Multiple gestations

- History of SPTB in a prior pregnancy
- Rupture of membranes at the time of randomization
- Known major fetal structural (i.e. defined as those that are lethal or require prenatal or postnatal surgery) or chromosomal abnormality
- Fetal death at the time of randomization
- Cerclage in situ at the time of randomization
- Pessary in situ at the time of randomization
- Vaginal bleeding at the time of randomization
- Women who are unconscious, severly ill, mentally handicapped, or under the age of 18 years.
- Placenta previa and/or accreta
- Ballooning of membranes outside the cervix into the vaginal or TVU CL = 0mm
- Painful and regular uterine contractions

We define prior SPTB as history of spontaneous preterm delivery between 16 0/7 and 36 6/7 weeks in a prior pregnancy.

Gestational age will be judged from the menstrual history and confirmed by measurement of fetal crown-rump length at a first trimester scan or the head circumference at the anatomy scan.

## QUALITY CONTROL AND HANDLING OF DATA

Information of the characteristics of the patients, including demographic data, measurements for calculation of the BMI, and obstetrical and medical histories, will be obtained from the patients at the time of the TVU CL scan and will be recorded directly on the CRFs. These will then be entered into a computer database and on the subject screening log in the study site file.

Data on pregnancy outcomes were obtained from hospital maternity records. In case of PTB, records were examined to determine whether the delivery was medically indicated (indicated PTB) or spontaneous. SPTB included either spontaneous onset of labor or PPROM.

Quality control of screening, handling of data, and verification of adherence to protocols will be performed on a regular basis by the trial coordinators.

The operators who will perform the TVU CL scan will have received extensive training and passed a practical examination administered by an expert to demonstrate their competence in cervical assessment (Fetal Medicine Foundation Certificate of Competence in Cervical Assessment).

## MEASUREMENT OF CERVICAL LENGTH

Before the TVU CL scan, women will be asked to empty the bladder, undress from the waist down and to lie on an examination bed. The CL will be measured by operators with certification of competence in the technique (Fetal Medicine Foundation Certificate of Competence in Cervical Assessment). The length of the cervix will be measured with a transvaginal real-time ultrasound probe (GE Health Care Endocavity Transducer; bandwidth 5-13 MHz; Voluson E8) placed in the anterior fornix of the vaginal. Endocervical canal length will be measured as the distance between the internal and external os, by using a straight line with calipers placed at the notches made by the internal os and external os. The image will be enlarged while visualizing the three landmarks simultaneously. This procedure will be repeated three times. After a baseline CL will be measured, fundal pressure will be applied for 30 seconds as a provocative maneuver. CL will be measured during and after the fundal pressure. Only the shortest CL measurement will be recorded. Each examination will be performed during a minimum of five minutes.

## INTERVENTION GROUP AND CONTROL GROUP MANAGEMENT

At the time of randomization, all women will undergo a speculum examination. Moreover, vaginal swabs will be taken from all women in both groups for bacteriological analysis. If the results will show infection, appropriate treatment will be given without delaying the insertion of the pessary in the study group. The pessary will be not removed in case of evidence of bacterial infection after device insertion.

All the cervical pessaries that will be used in the trial are certified by European Conformity (CE0482, MED/CERT ISO 9003/EN 46003; Dr Arabin, Witten, Germany).

All the pessaries will be inserted by the attendings, who had received practical training in the placement of the device. Pessary insertion training consists of a didactic session and a hands-on session. All staff will be required to demonstrate competence in pessary placement on a live model.

Women in the control group will receive the same obstetrical care as those in the study group. All the participants will be followed in outpatient settings every month until delivery. In the pessary group, a digital exam will be done at each of these monthly visits to assure proper pessary placement. At any follow-up visit, TVU CL and assessment of adverse events will be recorded. For TVU CL $\leq$20 mm, women in both groups will be all recommended vaginal progesterone 200mg suppositories daily until 36 6/7 weeks.

No bed rest or activity restriction will be recommended. Abstain from vaginal intercourse will also not recommended.

In the study group, the Arabin pessary will be placed at the time of randomization and will be removed during the 37th weeks (37 0/7 – 37 6/7) or early if clinically indicated. Reason for early removal includes active vaginal bleeding, preterm labor with persistent contractions and advanced dilatation despite tocolysis, severe discomfort, or subject request.

## RANDOMIZATION AND MASKING

After written informed consented will be obtained from the eligible participants, women will be randomly allocated in a 1:1 ratio to either the pessary group or control group. Women were randomized by a web-based system (randomization.com) using random blocks of 2,4 and 6 to receive the pessary or no pessary. Randomization will be stratified by CL (CL ≤20mm, CL >20mm – 25mm).

The randomization sequence will be prepared by an independent statistician (at Division of Statistics, Department of Law, Economics, Management and Quantitative Methods, University of Sannio, Benevento, Italy) and implemented by use of central telephone. The recruiters or the trial coordinator will not have access to the randomization sequence. The allocation code will not be disclosed after the patient's initials are confirmed. The study will be open label because of the nature of the intervention, but the outcome assessors, data collectors, and data analysts will blinded to the allocated treatment group.

## PRIMARY AND SECONDARY OUTCOMES

The primary outcome is SPTB <34 weeks

The secondary outcomes are:

- SPTB <37, <32, and <28 weeks

- Mean gestational age at delivery in weeks
- Mean latency in days (time from randomization to delivery)
- PPROM <34 weeks
- Mode of delivery
- Maternal side effects
- Chorioamnionitis (i.e. inflammation of the chorion and amnion by histopathological assessment after delivery)
- Birth weight
- NICU
- Neonatal death (i.e. death of a live-born baby within the first 28days of life)
- Perinatal death (either fetal or neonatal mortality)
- A composite of adverse perinatal outcome defined as at least one of the following:
    - NEC
    - IVH grade 3 or higher
    - RDS
    - BPD
    - ROP requiring therapy
    - Blood-culture proven sepsis
    - Neonatal death.

**SAMPLE SIZE**

The sample size calculation presented here is based on detecting an effect that produces 50% reduction in the overall incidence of spontaneous preterm delivery between randomization and

33 6/7 weeks from an anticipated 25% in the control group (i.e. singletons with short cervix with vaginal progesterone).

On the assumption that 60% of women with singleton gestations fulfilling the entry criteria agree to participate in the study and provide follow-up data, we would be to approach about 500 such women for a final sample size of 300 women. The power calculations of 300 women (150 per group) were undertaken by computer simulation.

At our institution, we perform about 3,000 deliveries per year. However, our hospital is the one of the few referral center in the Regione Campania (an area of about 55,000 deliveries per year) for PTB and most of the women with short TVU CL at the routine anatomy scan are referred to our institution. Therefore, we perform about 600 counselling per year on the risk of PTB in singleton gestations with short cervix, of them about 500 are singleton gestations without prior SPTB. Based on these data, we estimate a 2-year study period, 1 year for enrollment and 1 year for data analysis.

## STATISTICAL ANALYSIS AND REPORTING

Results will be presented according to the CONSORT statement.

### *Baseline data*

Baseline data on (LIST) for the intervention and control groups will be summarized for by the median and the interquartile range. Continous data will be summarized in terms of mean, SD, minimum, maximum, and quartiles. Attribute data will be summarized on terms of frequency counts and proportions

### *Primary analysis*

The primary analysis will be an intention to treat comparison of the treatment assigned at randomization. The treatment effect will be tested at the two-tailed 5% level. A 95% CI will be produced the OR of intervention/control group. The incidence of SPTB <34 weeks will quantified by the OR with 95% CI using the logistic regression allowing for cervical length as a covariate

***Secondary analysis***

The risk of SPTB <34 will be assessed with the use of Kaplan-Meier analysis, in which gestational age is the time scale and spontaneous delivery the event, and elective deliveries will be treated as censored. Hazard ratios will be estimated.

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS) (IBM Inc., Armonk, NY, USA)

## REGULATORY ISSUES

This study is approved by the local IRB at University of Naples Federico II (Comitato Etico Carlo Romano) (Unina trial #213/15)

## FUNDING

No financial support will be received for this study

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