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Comparison of the Efficacy of Emergency Two-level and Single Cervical Cerclage in Cervical Insufficiency in the Second Trimester of Pregnancy - Multicenter Prospective Randomized Trial
Cervical Occlusion Two-level Stitch Application (COSA)

Study Protocol and Statistical Analysis Plan
Unique Protocol ID: nr 5/2024

This is an open-label, multicentre, prospective, randomised controlled trial (RCT). Women diagnosed with cervical insufficiency with fetal membranes visible through open internal os between 16+0 and 25+6 weeks of gestation will be included to the study. The inclusion criteria consist of singleton pregnancy, gestational age 16+0 to 25+6 weeks, live fetus. The exclusion criteria are:

- preterm rupture of membranes,
- vaginal bleeding,
- regular uterine contractions,
- maternal fever,
- diagnosed fetal genetic disorders,
- diagnosed major fetal anomalies,
- multiple pregnancy,
- congenital uterine anomalies,
- fetal demice,
- maternal leukocyte count >20 million/microliter,
- maternal serum C-reactive protein concentration > 20 mg/L.

Each patient will have a vaginal swab for aerobic and anaerobic bacteria and fungi culture, as well as for mycoplasmas, chlamydia and ureaplasma performed. Each patient will be treated with progesterone (vaginally 2 x 100 mg per day) and empirical antibiotic therapy (ceftriaxone 2.0 g iv + clarithromycin 2 x 500 mg po + metronidazole 3 x 500 mg iv for 7 days). If specific pathogens will be detected, the antibiotic therapy will be modified according to the antibiogram. If the diagnosis of cervical insufficiency will be made >23 weeks of gestation a single course of corticosteroid therapy will be administered (betamethasone 2 x 12 mg im). Indomethacin will also be administered for 48 hours (starting the day of cerclage administration, indomethacin 2 x 75 mg po for 48 hours). In the ingle-level

cerclage arm McDonald suture will be administered. In the double-level cerclage arm two separate
sutures analogous to McDonald technique will be placed, one above the other approximately 1 cm
higher. After randomization in the operating theater under regional anesthesia, after vaginal disinfection and visualization of the cervix, McDonald cerclage will be administered. In case of fetal membranes bulging to the vagina the patient will be placed in the Trendelenburg position with filling the bladder with saline and / or amnioreduction. In double-level cerclage arm two separate sutures analogous to the McDonald technique will be places, one approximately 1 cm higher above the other.
After the operation patients will receive standard perinatal care and will be followed up until miscarriage or delivery. The time and mode of delivery, the occurrence of complications related to the
cerclage placement and neonatal outcomes will be analyzed.
In the only randomized trial evaluating the effectiveness of rescue sutures in comparison to conservative management and bed rest, the rate of deliveries before 34 weeks of gestation was 53%.
Assuming a reduction of deliveries before 34 weeks to 20%, based on the power analysis of the test, the
size of each group was calculated for 39 patients.
After ending recruitment and collection of data, statistical analysis will be performed. Variables will be described as median, interquartile range or number and percentage. The Mann–Whitney test and the Fisher's exact test will be used for the statistical analysis. p-values < 0.05 will be considered significant.