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Posted Date: 3 September 2024

doi: 10.20944/preprints202409.0141.v1

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Case Report

# Successful Resolution of Cervical Insufficiency after Administration of a Novel Triple Antibiotic Therapy: A Case Report

Serena Xodo <sup>1,\*</sup>, Bassma Benchikh <sup>2</sup>, Ginevra Battello <sup>2</sup>, Giovanni Baccarini <sup>1</sup>, Marta Angelini <sup>1</sup>, Maria Orsaria <sup>3</sup> and Lorenza Driul <sup>1,2,4</sup>

<sup>1</sup> Clinic of Gynecology and Obstetrics, Ospedale Santa Maria della Misericordia, Udine 3310, Azienda Sanitaria Universitaria Friuli Centrale

<sup>2</sup> Clinic of Gynecology and Obstetrics, University of Udine, Udine 33100

<sup>3</sup> Institute of Pathology, Academic Hospital "Azienda Sanitaria Universitaria Integrata di Udine", 33100, Udine, Italy

<sup>4</sup> Department of Medical Area (DAME), University of Udine, Udine 33100

\* Correspondence: serena.xodo@gmail.com

**Abstract:** Background: Cervical insufficiency, marked by recurrent painless cervix dilation leading to second-trimester pregnancy losses, is traditionally managed through cerclage placement and vaginal progesterone administration. However, a recent experimental approach targeted intra-amniotic inflammation or infection in a selected group of women with cervical dilation over 1 cm, intact membranes, and no uterine contractions in the second or third trimester. Case presentation: We report a case of a 21 year old primigravid woman who experienced resolution of mid-trimester cervical insufficiency after the administration of triple antibiotic therapy, as confirmed by ultrasound monitoring. Remarkably, the patient successfully carried the pregnancy to term and delivered a healthy baby. Conclusions: This case highlights the potential effectiveness of a novel combination of antibiotics, even in the presence of several high-risk pregnancy conditions, and underscores the possibility of a favorable outcome.

**Keywords:** cervical insufficiency; triple antibiotic therapy; cerclage; intra-amniotic infection; case report

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## Background

Cervical insufficiency (CI) is characterized by recurrent painless dilation of the cervix, leading to pregnancy losses in the second trimester [1]. According to the American College of Obstetricians and Gynecologists (ACOG), it is defined as "the inability of the uterine cervix to maintain a pregnancy in the second trimester, without the presence of clinical contractions, labor, or both" [2]. The diagnosis of CI can be established through obstetric history, particularly if a patient has a history of more than two consecutive second-trimester pregnancy losses or extremely preterm births before 28 weeks with minimal or no symptoms. Additionally, ultrasound findings can contribute to the diagnosis, revealing a cervical length (CL) of 25 mm or less before 24 weeks with no evidence of labor, infection, or bleeding. Physical examination can also be a diagnostic tool, as the cervix may appear dilated and effaced between 14 and 27 weeks of gestation in the absence of contractions. The recommended approach for CI management consists of cerclage placement in patients with recurrent second trimester losses preceded by painless cervical dilation, in patients with one prior spontaneous preterm birth and trans-vaginal ultrasound (TVU) CL  $\leq$  25 mm before 24 weeks in the current pregnancy and in women with CI assessed upon physical examination [3–5]. In each circumstance the vaginal administration of progesterone is recommended [6].

While the association between CI and intra-amniotic infection occurs quite often (8 – 52% of cases) when the cervix is  $\geq 2$  cm dilated on digital or speculum examination, this association is significantly reduced when the cervix is dilated less than 2 cm, even though sludge or biofilm is visible at ultrasound or membranes are exposed at speculum examination [7,8]. In these settings, the incidence of intra-amniotic infection is probably around 5 to 10% [9]. The use of amniocentesis is endorsed in order to exclude an intra-amniotic infection, which per se is a contraindication for cerclage placement [10]. Recently, a novel therapy has been attempted to treat the intra-amniotic inflammation or infection in a small group of women with cervical dilation more than 1 cm, intact membranes and no uterine contractions in the second or third trimester of pregnancy. This therapy consisted of the combination of ceftriaxone 1 g (intravenous) every 24 hours, clarithromycin 500 mg (oral) every 12 hours, and metronidazole (intravenous) 500 mg every 8 hours. Metronidazole was administered for a maximum of 4 weeks. Out of 22 women treated with this combination of antibiotics, the eradication of intra-amniotic inflammation/infection has been demonstrated to occur in 75% of cases, and the overall treatment success, defined as resolution of intra-amniotic infection/inflammation or delivery  $\geq 34$  weeks, happened in 59% of cases [11].

In the present study, we report a case of a 22-year-old patient in which the administration of the triple antibiotic therapy resolved a mid-trimester CI, as demonstrated by ultrasound controls.

### Case Presentation

We describe a case of a 21 year old primigravid South-American patient, who came at the clinic of Obstetrics and Gynecology of the university hospital of Udine at 20 weeks + 2 days of gestation for urgent evaluation, after an accidental fall at home. Upon arrival at our clinic, the patient denied a direct trauma on the abdomen. She reported no dizziness and no abnormal vaginal discharge. She only complained pelvic pain. Her family history was not known, since she reported to be adopted. Her personal history lacked significant pathologic conditions. She had a spontaneous singleton pregnancy, without medical complications until that moment. A first trimester ultrasound scan confirmed that the fetal crown rump length was coherent with the menstrual cycle indicated by the woman. The first trimester combined test revealed a fetal low risk for common trisomies (21, 18 and 13). However, the speculum examination showed a protrusion of the amniotic sac from the external uterine orifice, with no bleeding or fluid pooling. For this reason, the on duty physician decided to not perform a TVU. On transabdominal sonographic examination, the cervix appeared short, with a length of 4 mm. Moreover, the fetus was alive, the placenta and the amniotic fluid were described respectively as posterior and regular. Given the CI, the patient was admitted to the clinic. Two days after, the patient underwent an anomaly scan which demonstrated a fetus without structural anomalies, with a normal growth; no irregularities were seen in the placenta. However, sludge was reported in the amniotic fluid. On that occasion a speculum examination was repeated, which confirmed the amniotic sac protrusion from the cervix, and the TVU showed a cervical dynamic condition, ranging from a closed cervix with a 9 mm cervical length and a wide funneling to an open cervix with bulging membranes under Valsalva maneuver. The woman was informed about the poor prognosis that usually accompanies a diagnosis of CI. She was offered an amniocentesis in order to assess the presence of an intra-amniotic infection or inflammation, which is a contraindication to the cerclage placement. However, she refused any intervention that might potentially compromise the fetal wellbeing further. Finally, the study of Kyung Joon et al. [10] was illustrated and explained to the woman and her mother, and we gave her the possibility to try the triple antibiotic therapy for a period of at least 10 days. After this counseling, therapy was accepted and started. This treatment included the administration of three different antibiotics, specifically ceftriaxone 1 gram intravenous once a day, metronidazole 500 mg intravenous 3 times a day and clarithromycin 1 g orally 2 times a day. At the same time, progesterone therapy was started intramuscularly, once a week. During hospitalization the patient was instructed to adopt the Trendelenburg position as much as possible; therefore, prophylaxis with low molecular weight heparin was also initiated. The triple antibiotic therapy was continued for 14 days. No maternal adverse reactions were observed during the period of therapy administration. Prophylaxis with corticosteroids was also given in order to accelerate fetal

lung maturation given the risk of preterm birth. During hospitalization the endocervical swabs turned out to be positive for *Streptococcus Agalactiae*, while urine cultures and urinalysis were negative. After therapy end, the woman was carefully monitored showing no alarming symptoms, such as uterine contractions or vaginal blood or fluid discharge. Moreover, the speculum inspection revealed a closed cervix with no protrusion of the sac into the vagina. Surprisingly, at 24 weeks and 6 days of gestation the cervix length measured 21.7 mm at TVU and sludge was not evident anymore. Therefore, after one month and a half, the woman was discharged from our clinic.

Once discharged, the woman continued anticoagulation as well as vaginal progesterone and oral iron supplementation. She was strictly followed either by her attending Obstetrician and in our Ambulatory for high risk pregnancy. Due to positivity for *Ureaplasma parvum* and *Staphylococcus aureus* of rectal and endocervical swabs performed at the discharge time, a therapy with oral azithromycin 1 gr for 6 days and a metronidazole/clotrimazole cream was given to the patient. The next pregnancy follow up confirmed a regular fetal growth and a stable cervical length.

Unexpectedly, the patient reached the term of gestation. She was again admitted due to labor onset at 40 weeks and 1 day of gestation. To correct dynamic dystocia, labor was augmented through Oxytocin infusion. Moreover, upon maternal request, epidural analgesia was carried out. Due to persistent positivity of vaginal-rectal swabs for *Streptococcus Agalactiae* intravenous ampicillin was administered, according to the local protocol. The patient underwent a cesarean delivery for failed fetal head engagement in maternal pelvis. At 40 weeks and 2 days of gestation a male, healthy neonate weighing 3556 grams was born. The postpartum course of both mother and infant was regular and there were no complications. Therapy with enoxaparin 4000 IU was continued at home for 10 days as per local protocol after cesarean delivery. The histological examination revealed the presence of focal siderophages within the fetal membranes and the presence of minimal acute and chronic inflammatory infiltrates within the subchorionic fibrinoid deposition in the placental plate.

## Discussion

This case demonstrates the successful resolution of a severe mid-trimester CI associated with amniotic fluid sludge after a novel combination of three antibiotics administered to the mother for 14 days. This therapy was first described in a retrospective study including 22 women with single pregnancy, intact membranes and a painless cervical dilatation of  $> 1$  cm between 16 and 28 weeks of gestation. All women had a diagnosis of intra-amniotic infection or inflammation after transabdominal amniocentesis that was treated with a regimen including ceftriaxone, clarithromycin, and metronidazole. Of the 22 patients, six delivered within one week of amniocentesis, while the remaining 16 delivered at 37 weeks on average. Among these, twelve accepted to undergo a repeat amniocentesis, which proved the eradication of the intra-amniotic infection/inflammation in 9 cases. Of the 4 patients who did not have a follow-up invasive procedure all delivered at or beyond 34 weeks of gestation [10]. In 2022 another interesting report was published describing a patient with mid-trimester CI and evidence of sterile intra-amniotic inflammation, who was given the triple antibiotic therapy. After the end of therapy the sonographic and speculum examinations demonstrated the resolution of CI. The fact that this patient underwent a planned cesarean delivery at near term of gestation demonstrated that, in cases with high risk of pregnancy loss due to CI associated with inflammation of the amniotic cavity, a successful outcome is possible [8]. Our case accounts in the literature as the 24th patient that received the triple antibiotic therapy with the aim to resolve a CI. However, contrary to previous cases, we did not perform the amniocentesis, according to the patient's request. This is an important discussion issue from different points of view. First, there is the clinician's perspective that highlights the importance of having a diagnosis of intra-amniotic infection or inflammation, which per se contraindicates a rescue cerclage placement and significantly worsens the pregnancy outcome [12]. Second, there is the patient's point of view, who does not always accept an invasive procedure, given its additional risk to further compromise the fetal health. Notably, this risk might be increased if the diagnosis of CI occurs at around 22-23 gestational weeks, when the fetus is potentially capable of extrauterine life. When dealing with fetal conditions, the available options span a broad spectrum, from a conservative approach to active

intervention, and in certain cases, the consideration of pregnancy termination. It is imperative for healthcare providers to fulfill their ethical duty by thoroughly discussing all potential avenues with the patient and her family during counseling sessions, ensuring a truly informed consent. Given the intricate nature, uncertainties, and possible controversies surrounding these conditions, physicians must be vigilant to prevent the patient's decision-making from being swayed by undue optimism or pessimism [13].

Interestingly, we observed the presence of sludge before starting the antibiotic therapy, but at the end not anymore. Recently, the role of amniotic fluid sludge has gained increasing attention in the literature. A systematic review published in 2020, after analyzing 17 studies for a total of 2432 women, showed that patients with amniotic fluid sludge had an increased incidence of preterm delivery before 37 weeks [14]. Another study analyzed women with sonographic evidence of sludge in the amniotic fluid through amniocentesis ranging from 18 to 41 weeks of gestation. This study found that samples collected before 33 weeks of gestation had a pus-like appearance, thus a process with infectious or inflammatory origin; whereas after this gestational age most of the samples appeared to be consistent with vernix, which is linked to fetal maturation [15]. Theoretically, the sludge disappearance after triple antibiotic therapy in our patient could be interpreted as an indirect sign of the successful eradication of the intra-amniotic infection or inflammation. Moreover, the Pathologist noted the occurrence of focal siderophages in fetal membranes and observed minimal acute and chronic inflammatory infiltrates within the subchorionic fibrinoid deposition in the placental plate. These findings might suggest that the initial intra-amniotic infection or inflammation detected during the diagnosis of CI may have resolved or, at the very least, did not progress further.

Another issue raised by this case report was the impossibility to perform the amniocentesis because of consent refusal. Currently, there is no non-invasive antenatal diagnostic test in clinical practice for intra-amniotic infection or inflammation that is recognized safe and acceptable to women. A recent study noted a correlation between intra-amniotic and vaginal IL-6 in patients with CI and bulging membranes during the second trimester of pregnancy. However, the authors claimed for further studies to assess whether an amniocentesis could be avoided before an emergency cerclage [16].

According to the ACOG guidelines, in patients with a physical examination based diagnosis of CI before 24 weeks, a rescue cerclage after an amniocentesis to rule out intra-amniotic infection is preferred rather than the expectant management. Supplementation with progesterone is also suggested, but no antibiotics are administered [2]. However, in this case we opted for a conservative management, including a novel combination of antibiotics based on previous enthusiastic reports and pharmacokinetic studies [8,10,17–19].

The rationale underscores the inadequacy of erythromycin or azithromycin in eliminating intra-amniotic infection with *Ureaplasma* species, which is a prevalent microorganism in the amniotic fluid of individuals at risk for preterm birth. This inadequacy is attributed to their limited trans-placental passage, resulting in suboptimal antimicrobial activity in the amniotic fluid (with only 3% of erythromycin and 2.6% of azithromycin crossing the placenta). In contrast, clarithromycin exhibits a significantly higher transplacental passage rate, proving effective against intra-amniotic infection with *Ureaplasma* species [17]. The inclusion of metronidazole is justified by its potent action against anaerobic bacteria, frequently implicated in intra-amniotic infection, but often difficult to identify through cultivation techniques [18]. Ceftriaxone is integrated for its broad coverage of aerobic bacteria and impressive transplacental passage rate [19].

## Conclusions

To conclude, recent findings underscore the efficacy of antibiotics in addressing intra-amniotic infection/inflammation with CI scenarios. Within this context, we present a case wherein the strategic administration of antibiotic therapy led to the resolution of mid-trimester CI, despite the presence of sterile intra-amniotic inflammation and amniotic fluid sludge. This underscores the potential therapeutic impact of antibiotics in such complex clinical scenarios.

**Author Contributions:** Conceptualization: Serena Xodo and Lorenza Driul; methodology: Serena Xodo and Bassma Benchick; validation: Giovanni Baccarini, Marta Angelini and Lorenza Driul; writing—original draft preparation: Serena Xodo and Bassma Benchick; writing—review and editing: all authors; supervision: Giovanni Baccarini, Marta Angelini and Lorenza Driul. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The case presentation was reviewed and approved by the Institutional Review Board (IRB), Department of Medical Area, University of Udine.

**Informed Consent Statement:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Data Availability Statement:** The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

**Conflicts of Interest:** The authors declare that they have no competing interests.

### List of Abbreviations

Cervical insufficiency	(CI)
American College of Obstetricians and Gynecologists	(ACOG)
cervical length	(CL)
trans-vaginal ultrasound	(TVU)

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