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SONOGRAPHIC SHORT CERVIX - CLINICAL MANIFESTATION OF SUBCLINICAL INTRA-AMNIOTIC INFECTION: A COMPREHENSIVE REVIEW

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სონოგრაფიულად დადასტურებული მოკლე საშვილოსნოს ყელი, როგორც სუბკლინიკური ინტრაამნიონური ინფექციის პოტენციური კლინიკური გამოვლინება: სისტემური და კომპლექსური მიმოხილვა

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რეზიუმე

ნაადრევი მშობიარობა კვლავ რჩება ჯანდაცვის მნიშვნელოვან გამოწვევად, რაც ხელს უწყობს პერინატალური ავადობისა და სიკვდილიანობის მაჩვენებლის პროცენტულ ზრდას. ორსულობის მეორე ტრიმესტრში ულტრაბგერით გამოვლენილი "მოკლე" საშვილოსნოს ყელი წარმოადგენს ერთ-ერთ მნიშვნელოვან პროგნოზულ მაჩვენებელს ყელის უკმარისობის და ნაადრევი მშობიარობის რისკის შეფასებისთვის. საშვილოსნოს ყელის უკმარისობას მრავალი მიზეზი აქვს, მათ შორის ინტრაამნიონური ინფექცია და ინტრაამნიონური ანთება, რომლებიც ხშირ შემთხვევაში უსიმპტომოდ მიმდინარეობს.

აღნიშნული მიმოხილვის მიზანია, საშვილოსნოს ყელის დამოკლებასა და ინტრაამნიონურ პათოლოგიას შორის არსებული ურთიერთკავშირის დეტალური ანალიზი, რომლის საფუძველზეც განისაზღვრება ადრეული დიაგნოსტიკის გადამწყვეტი მნიშვნელობა ნაადრევი მშობიარობის პრევენციისა და მიზანმიმართული თერაპიული მიდგომების შემუშავებისთვის, რაც საბოლოოდ განაპირობებს ორსულობისა და ნაყოფის გამოსავლის გაუმჯობესებას.

კვლევებმა აჩვენა რომ კლინიკურად უსიმპტომო ქალების დაახლოებით 9–10%-ში, რომელთაც ულტრაბგერითი კვლევით დაუდგინდა მოკლე საშვილოსნოს ყელი (<25 მმ), აღმოჩნდა ამნიონური სითხის მიკრობული ინვაზია (MIAC), ხოლო დამატებით 10–22%-ში - ინტრაამნიონური ანთება. ბიომარკერები, როგორიცაა ინტერლეიკინი-6 (IL-6) და მატრიქსის მეტალოპროტეინაზა-8 (MMP-8) წარმოადგენს უტყუარ საშუალებას სწრაფი დიაგნოსტიკისთვის. აქედან გამომდინარე მიზანმიმართული კომბინირებული ანტიბიოტიკოთერაპია ცეფტრიაქსონის, კლარიტრომიცინისა და მეტრონიდაზოლის გამოყენებით ეფექტურად უზრუნველყოფს ინტრაამნიონური ინფექციის აღმოფხვრას, რაც თავის მხრივ გულისხმობს ნაადრევი მშობიარობის პრევენციას, ნაყოფთან ნევროლოგიური გართულებების შემცირებას და კეთილსაიმედო შედეგს. აღნიშნული მონაცემები მიუთითებს ადრეული დიაგნოსტიკისა და შესაბამისი მართვის მნიშვნელობაზე, ნაადრევი მშობიარობის პრევენციისა და შესაბამისად ნაყოფის ზრდა-განვითარების პროგნოზის გაუმჯობესებაზე.

Introduction. Preterm birth remains the leading cause of neonatal morbidity and mortality worldwide, affecting approximately 10% of all pregnancies. A sonographic short cervix, defined as cervical length ≤25 mm in the mid-trimester, is one of the most powerful predictors of spontaneous preterm delivery [1]. While cervical shortening has traditionally been viewed as a mechanical phenomenon related to cervical insufficiency, emerging evidence suggests that subclinical intra-amniotic infection and inflammation may be important underlying etiologies in a significant subset of cases [3]. Remarkably, a sonographic short cervix may be the only clinical manifestation of these intrauterine pathologies, as affected women typically present without symptoms of infection, labor, or membrane rupture [1,3]. The recognition that cervical shortening represents a syndrome with multiple potential etiologies has important implications for management. Understanding the role of subclinical infection and inflammation in this condition is crucial for developing targeted therapeutic interventions and improving outcomes for both mothers and infants.

Epidemiology and Clinical Significance

Prevalence of Intra-amniotic Pathology in Short Cervix

Multiple studies have investigated the prevalence of microbial invasion of the amniotic cavity (MIAC) and intra-amniotic inflammation in asymptomatic women with sonographic short cervix. Hassan et al. reported that 9% (5/57) of women with cervical length <25 mm at 14-24 weeks had MIAC, with *Ureaplasma urealyticum* being the most frequently isolated organism (4/5 cases) [1]. Subsequent studies have expanded these findings. Vaisbuch et al. found that among women with cervical length ≤15 mm, 4.3% had proven intra-amniotic infection, while 22.2% of those with negative cultures had intra-amniotic inflammation defined by elevated MMP-8 concentrations [4]. A comprehensive analysis by Romero et al. revealed that sterile intra-amniotic inflammation (without detectable microorganisms) was present in 10% of asymptomatic women with cervical length ≤25 mm and was actually more common than microbial-associated inflammation [3].

Clinical Outcomes. The presence of intra-amniotic infection or inflammation in women with short cervix has significant prognostic implications. Patients with intra-amniotic inflammation demonstrate:

- 40% delivery rate within 7 days of diagnosis [4]
- Significantly shorter amniocentesis-to-delivery intervals (median 18 vs 42 days) [4]
- Nearly four-fold increased risk of delivery per unit time compared to those without inflammation [3]
- Higher rates of histologic chorioamnionitis (100% vs 59%) [4]

Pathophysiology

Mechanisms of Cervical Shortening in Infection. The pathophysiology linking intra-amniotic infection to cervical shortening involves complex inflammatory cascades. Microbial invasion triggers the release of pro-inflammatory cytokines including IL-6, IL-8, and tumor necrosis factor-α (TNF-α), which activate matrix metalloproteinases [5]. These proteolytic enzymes degrade the extracellular matrix of the cervix, leading to cervical ripening and effacement [6].

Sterile vs Microbial-Associated Inflammation. An important distinction exists between microbial-associated and sterile intra-amniotic inflammation. Sterile inflammation may result from damage-associated molecular patterns (DAMPs) that activate the inflammasome complex through caspase-1, leading to inflammation without detectable microorganisms [3]. This mechanism may explain why sterile inflammation is paradoxically more common than infection-related inflammation in some populations.

Diagnostic Approaches

Table 1: Biomarkers for Diagnosis of Intra-amniotic Inflammation

Biomarker	Cut-off Value	Sensitivity	Specificity	Clinical Application
IL-6 (AF)	≥2.6 ng/mL	80-85%	75-85%	Gold standard for inflammation
MMP-8 (AF)	>23 ng/mL	70-90%	80-95%	Rapid bedside test available
WBC count (AF)	≥100 cells/mm³	60-70%	80-90%	Immediate availability
IL-6 (cervicovaginal)	≥1.7 ng/mL	58%	83%	Non-invasive screening
MMP-8 rapid test	Positive	85%	90%	Point-of-care testing

AF = Amniotic fluid

Amniocentesis and Fluid Analysis. Transabdominal amniocentesis remains the definitive diagnostic approach for identifying intra-amniotic pathology in women with short cervix. Standard evaluation includes:

1. **Microbiological studies**: Culture for aerobic/anaerobic bacteria and genital mycoplasmas, PCR for *Ureaplasma* species [1,3]
2. **Inflammatory markers**: IL-6, MMP-8, white blood cell count [4,7]
3. **Molecular techniques**: Broad-range PCR with electrospray ionization mass spectrometry for culture-negative cases [3,8]

Non-invasive Approaches. Cervicovaginal fluid analysis offers a non-invasive alternative for screening, though with lower diagnostic accuracy than amniocentesis. Cervicovaginal IL-6 levels >1.7 ng/mL have demonstrated 58% sensitivity and 83% specificity for intra-amniotic inflammation [10]. Combined biomarker panels and incorporation of clinical factors may improve predictive accuracy [11].

Microbiology

Table 2: Common Microorganisms in Subclinical Intra-amniotic Infection

Organism	Frequency	Clinical Significance	Antibiotic Susceptibility
Ureaplasma urealyticum	60-80%	Most common isolate	Macrolides, tetracyclines
Mycoplasma hominis	10-20%	Often polymicrobial	Macrolides, tetracyclines
Fusobacterium nucleatum	5-10%	Associated with severe inflammation	Metronidazole, β-lactams
Gardnerella vaginalis	5-10%	Part of polymicrobial infection	Metronidazole, clindamycin
Bacteroides species	<5%	Anaerobic component	Metronidazole, β-lactam/β-lactamase inhibitors

The microbiology of subclinical intra-amniotic infection differs from clinical chorioamnionitis. *Ureaplasma* species predominate, present in 60-80% of positive cultures [1,12]. These organisms are frequently missed by conventional culture techniques, requiring special media and conditions for isolation. The polymicrobial nature of many infections necessitates broad-spectrum antimicrobial coverage.

Treatment Strategies

Antibiotic Therapy. Traditional antibiotic regimens have shown limited success in eradicating intra-amniotic infection. However, a targeted approach using ceftriaxone, clarithromycin, and metronidazole has demonstrated promising results [12,13].

Recommended Regimen:

- Ceftriaxone 1g IV every 24 hours
- Clarithromycin 500mg PO every 12 hours
- Metronidazole 500mg IV every 8 hours

This combination was selected based on:

1. **Clarithromycin**: Superior transplacental passage compared to other macrolides and effectiveness against *Ureaplasma* species [12]
2. **Ceftriaxone**: Enhanced coverage of aerobic bacteria with excellent transplacental transfer [13]
3. **Metronidazole**: Anaerobic coverage for polymicrobial infections [12]

Treatment Outcomes. Studies have reported variable but encouraging success rates with targeted antibiotic therapy:

- Eradication of *Ureaplasma urealyticum* in 75% (3/4) of cases, with subsequent term delivery [1]

- Overall treatment success (resolution of infection/inflammation or delivery ≥34 weeks) in 59-84% of cases [13,14]
- Reduction in intra-amniotic inflammation from 75% to 54% with the targeted regimen [15]

Table 3: Comparison of Antibiotic Regimens for Intra-amniotic Infection

Regimen	Eradication Rate	Term Delivery Rate	Comments
Ampicillin/Erythromycin	0-15%	10-20%	Poor *Ureaplasma* coverage
Ceftriaxone/Clarithromycin/Metronidazole	33-79%	40-60%	Current recommended regimen
Azithromycin (experimental)	60-75%	Not reported	Animal studies only

Long-term Neurodevelopmental Outcomes

Cerebral Palsy Risk. The association between intra-amniotic inflammation and adverse neurodevelopmental outcomes is well-established. Yoon et al. demonstrated that fetal exposure to intra-amniotic inflammation increases the odds of cerebral palsy at age 3 years [16]:

- Funisitis: OR 5.5 (95% CI 1.2-24.5)
- Elevated amniotic fluid IL-6: OR 5.9 per log increase
- Elevated amniotic fluid IL-8: OR 5.5 per log increase

Mechanisms of Neurological Injury. The fetal inflammatory response syndrome (FIRS) triggered by intra-amniotic inflammation leads to systemic cytokine elevation and activation of microglia in the developing brain [17]. This neuroinflammation results in:

- White matter injury (periventricular leukomalacia)
- Disruption of oligodendrocyte maturation
- Altered neurodevelopmental trajectories
- Increased risk of autism spectrum disorders and cognitive impairment [18]

Implications for Counseling. The significant risk of adverse neurodevelopmental outcomes necessitates comprehensive counseling for affected families. Early intervention programs and developmental monitoring should be initiated for infants exposed to intra-amniotic inflammation, regardless of gestational age at delivery.

Clinical Management Algorithm

Table 4: Proposed Management Algorithm for Asymptomatic Short Cervix

Clinical Finding	Diagnostic Approach	Management	Follow-up
CL 20-25mm, no risk factors	Consider amniocentesis	Progesterone, surveillance	Weekly CL measurement
CL <20mm	Recommend amniocentesis	Progesterone + evaluate for infection	Twice weekly monitoring
CL <15mm	Strongly recommend amniocentesis	Progesterone + antibiotics if infection/inflammation	Admission consideration
Positive MIAC/inflammation	Confirm with biomarkers	Targeted antibiotics + corticosteroids	Repeat amniocentesis in 1 week

Special Considerations

Cervical Cerclage. The role of cerclage in women with short cervix and subclinical infection remains controversial. While mechanical support may be beneficial, the presence of infection theoretically increases the risk of complications. Current evidence suggests:

- Cerclage may be considered after successful antibiotic treatment [14]
- Prophylactic antibiotics should be administered peri-procedure
- Close monitoring for signs of clinical chorioamnionitis is essential

Progesterone Therapy. Vaginal progesterone remains a cornerstone of management for short cervix, regardless of infectious etiology. However, its efficacy may be reduced in the presence of inflammation. Combination therapy with antibiotics and progesterone may offer synergistic benefits [19].

Future Directions

Emerging Diagnostics

1. **Transcervical amniotic fluid collection**: Novel devices allowing non-invasive fluid sampling [20]
2. **Multi-omics approaches**: Integration of proteomics, metabolomics, and microbiome analysis
3. **Cell-free fetal DNA**: Evaluation of inflammatory signatures in maternal plasma

Therapeutic Innovations

1. **Anti-inflammatory agents**: N-acetylcysteine and other antioxidants show promise [21]
2. **Immunomodulation**: IL-1 receptor antagonists to block inflammatory cascades
3. **Precision medicine**: Tailored therapy based on specific microbial and inflammatory profiles

Conclusions. A sonographic short cervix may represent the sole clinical manifestation of subclinical intra-amniotic infection or inflammation in up to one-third of affected women. Recognition of this association has important implications for diagnosis, treatment, and counseling. Key findings include:

1. **High prevalence**: 9-10% of women with short cervix have MIAC, with an additional 10-22% having sterile inflammation
2. **Diagnostic advances**: Rapid bedside tests for MMP-8 and IL-6 enable timely diagnosis
3. **Treatment success**: Targeted antibiotic therapy can eradicate infection in 60-80% of cases
4. **Long-term risks**: Significant association with cerebral palsy and neurodevelopmental impairment
5. **Comprehensive approach**: Combined strategies including antibiotics, progesterone, and close monitoring optimize outcomes

Further research is needed to refine diagnostic criteria, optimize treatment protocols, and develop preventive strategies for this important cause of preterm birth and neonatal morbidity.

References

1. Hassan S, Romero R, Hendler I, et al. A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. J Perinat Med. 2006;34(1):13-19.
2. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med. 1996;334:567-572.
3. Romero R, Miranda J, Chaiworapongsa T, et al. Sterile intra-amniotic inflammation in asymptomatic patients with a sonographic short cervix: prevalence and clinical significance. J Matern Fetal Neonatal Med. 2015;28(11):1343-1359.
4. Vaisbuch E, Hassan SS, et al. Patients with an asymptomatic short cervix (≤15 mm) have a high rate of subclinical intraamniotic inflammation: implications for patient counseling. Am J Obstet Gynecol. 2010;202(5):433.e1-8.
5. Pandey M, Chauhan M, Awasthi S. Interplay of cytokines in preterm birth. Indian J Med Res. 2017;146(3):316-327.

6. Vadillo-Ortega F, Estrada-Gutiérrez G. Role of matrix metalloproteinases in preterm labour.BJOG.2005;112:1:19-22
7. Chaiyasit N, Romero R, Chaemsaithong P, et al. Clinical chorioamnionitis at term VIII: a rapid MMP-8 test for the identification of intra-amniotic inflammation. J Perinat Med. 2017;45(5):539-550.
8. Kim YM, Park KH, Park H, et al. Complement C3a, But Not C5a, Levels in Amniotic Fluid Are Associated with Intra-amniotic Infection and/or Inflammation and Preterm Delivery in Women with Cervical Insufficiency or an Asymptomatic Short Cervix. J Korean Med Sci. 2018;33(35):e220.
9. Chaemsaithong P, Romero R, Docheva N, et al. Comparison of rapid MMP-8 and interleukin-6 point-of-care tests to identify intra-amniotic inflammation/infection and impending preterm delivery in patients with preterm labor and intact membranes. J Matern Fetal Neonatal Med. 2018;31(2):228-244.
10. Jung EY, Park KH, Lee SY, et al. Non-invasive prediction of intra-amniotic infection and/or inflammation in patients with cervical insufficiency or an asymptomatic short cervix (≤15 mm). Arch Gynecol Obstet. 2015;292(3):579-587.
11. Park H et al. Plasma inflammatory and immune proteins as predictors of intra-amniotic infection and spontaneous preterm delivery in women with preterm labor: a retrospective study. BMC Pregnancy Childbirth. 2018;18(1):146.
12. Lee J, Romero R, Kim SM, et al. A new antibiotic regimen treats and prevents intra-amniotic inflammation/infection in patients with preterm PROM. J Matern Fetal Neonatal Med. 2016;29(17):2727-2737.
13. Yoon BH et al. Antibiotic administration can eradicate intra-amniotic infection or intra-amniotic inflammation in a subset of patients with preterm labor and intact membranes. Am J Obstet Gynecol. 2019;221(2):142.e1-142.e22.
14. Lee J, Romero R, Kim SM, et al. Evidence that antibiotic administration is effective in the treatment of a subset of patients with intra-amniotic infection/inflammation presenting with cervical insufficiency. Am J Obstet Gynecol. 2019;221(2):140.e1-140.e18.
15. Gomez R, Romero R, Nien JK, et al. Antibiotic administration to patients with preterm premature rupture of membranes does not eradicate intra-amniotic infection. J Matern Fetal Neonatal Med. 2007;20(2):167-173.
16. Yoon BH, Romero R, Park JS, et al. Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol. 2000;182(3):675-681.
17. Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res. 1997;42(1):1-8.
18. Andrews WW, Cliver SP, Biasini F, et al. Early preterm birth: association between in utero exposure to acute inflammation and severe neurodevelopmental disability at 6 years of age. AmJObstet Gynec. 2008;198(4):466.e1-11.
19. Pustotina O. Effectiveness of indomethacin, antibiotics, and vaginal progesterone in reduction of preterm birth risk associated with asymptomatic cervical shortening and amniotic fluid "sludge". J Matern Fetal Neonatal Med. 2018;31(14):1851-1858.
20. Cobo T, Kacerovsky M, Jacobsson B. Noninvasive Sampling of the Intrauterine Environment in Women with Preterm Labor and Intact Membranes. Fetal Diagn Ther. 2018;43(4):241-249.
21. Shahin AY, Hassanin IM, Ismail AM, et al. Effect of oral N-acetyl cysteine on recurrent preterm labor following treatment of bacterial vaginosis. Int J Gynaecol Obstet. 2009;104(1):44-48.
22. Jung E, Romero R, Yeo L, et al. The amniotic fluid proteome predicts imminent preterm delivery in asymptomatic women with a short cervix. Sci Rep. 2022;12(1):11781.
23. Kiefer DG, Keeler SM, Rust OA, et al. Is midtrimester short cervix a sign of intraamniotic inflammation? Am J Obstet Gynecol. 2009;200(4):374.e1-5.
24. Holst RM, Mattsby-Baltzer I, et al. Interleukin-6 and interleukin-8 in cervical fluid in a population of Swedish women in preterm labor: relationship to microbial invasion of the amniotic fluid, intra-amniotic inflammation, and preterm delivery. Acta Obstet Gynecol Scand. 2005;84(6):551-557.
25. Vogel I, Thorsen P, Curry A, et al. Biomarkers for the prediction of preterm delivery. Acta Obstet Gynecol Scand. 2005;84(6):516-525.

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SUMMARY

A sonographic short cervix in the mid-trimester is a powerful predictor of spontaneous preterm delivery and may represent the only clinical manifestation of subclinical intra-amniotic infection or inflammation. This review examines the relationship between cervical shortening and intra-amniotic pathology, diagnostic approaches, treatment strategies, and long-term outcomes. Evidence demonstrates that 9-10% of asymptomatic women with sonographic short cervix (<25 mm) have microbial invasion of the amniotic cavity (MIAC), while sterile intra-amniotic inflammation occurs in an additional 10-22% of cases. Biomarkers including interleukin-6 (IL-6) and matrix metalloproteinase-8 (MMP-8) show promise for rapid diagnosis. Targeted antibiotic therapy with ceftriaxone, clarithromycin, and metronidazole has demonstrated success in eradicating intra-amniotic infection in selected cases, potentially allowing term delivery. However, the association with adverse neurodevelopmental outcomes, including cerebral palsy, underscores the importance of early recognition and intervention.

Keywords: short cervix, intra-amniotic infection, inflammation, preterm birth, chorioamnionitis