"Impact of undifferentiated connective tissue dysplasia on the development of cervical insufficiency and the risk of preterm birth."

Bayramov Sabir Djabrailovich
https://orcid.org/0000-0002-4219-0522
Republican Perinatal Center

Sultanov Saidazim Nasirovich
Doctor of Medical Sciences, Professor, Chief Physician of the 'Ayolcare' Clinic"
dr.sabirendo@gmail.com

Abstract: Isthmic-cervical insufficiency (ICI) remains a major contributor to preterm birth during the second and third trimesters. Increasing attention has recently been directed toward functional forms of ICI, which are thought to arise from systemic abnormalities of connective tissue. This study presents findings from a prospective analysis evaluating the contribution of undifferentiated connective tissue dysplasia (uCTD) to the development of ICI and preterm birth. A total of 114 pregnant patients diagnosed with ICI were assessed and stratified into three groups based on the presence and degree of uCTD. The study demonstrated that uCTD correlates with disturbed collagen metabolism, earlier cervical shortening, and unfavorable pregnancy outcomes. The results support the pathogenic role of uCTD in functional ICI and highlight the importance of early identification of connective tissue dysfunction. Keywords: isthmic-cervical insufficiency, undifferentiated connective tissue dysplasia, preterm birth, hydroxyproline, magnesium.

Keywords: cervical insufficiency, undifferentiated connective tissue dysplasia, preterm birth, hydroxyproline, magnesium.

Introduction.

Preterm birth remains one of the most significant challenges in modern obstetrics, contributing substantially to perinatal morbidity and mortality. Despite the implementation of new diagnostic and preventive strategies, the rate of pregnancy loss in the second and third trimesters remains consistently high. Isthmic-cervical insufficiency is a major factor within this spectrum of complications, often developing without clinical symptoms and being diagnosed only after its manifestations become evident. Traditionally, cervical insufficiency has been viewed primarily as a consequence of anatomical injury to the cervix. However, in recent years increasing attention has been given to functional forms of cervical insufficiency that develop in the absence of pronounced structural abnormalities. This highlights the involvement of systemic factors that determine the biomechanical properties of the cervix during gestation. One such factor is undifferentiated connective tissue dysplasia, a systemic condition characterized by impaired synthesis and remodeling of extracellular matrix

components. Because the cervix is largely composed of connective tissue, structural alterations associated with uCTD may contribute to premature cervical ripening and the development of cervical insufficiency. Despite the growing interest in this issue, the role of uCTD in the pathogenesis of cervical insufficiency and preterm birth remains insufficiently explored and requires further clinical and pathogenetic investigation.

Materials and Methods The study was conducted as a prospective observational investigation and included 114 pregnant women diagnosed with cervical insufficiency in the second trimester of gestation. The diagnosis of cervical insufficiency was established based on transvaginal ultrasound cervicometry findings (cervical length ≤25 mm before 24 weeks of pregnancy and/or the presence of V- or U-shaped funneling of the internal os).

The patients were divided into three groups according to the presence and severity of undifferentiated connective tissue dysplasia: • **Group I (n=51):** pregnant women with cervical insufficiency and no signs of uCTD • **Group II (n=47):** pregnant women with cervical insufficiency and mild uCTD • **Group III (n=16):** pregnant women with cervical insufficiency and moderate or severe uCTD

Assessment of uCTD was performed using a modified scoring system that incorporated clinical and anamnestic features. As biochemical markers of connective tissue metabolism, daily urinary hydroxyproline levels and serum magnesium concentrations were measured. Statistical analysis was carried out using standard methods of variational statistics, and differences were considered significant at $p<0.05$.

Results

Undifferentiated connective tissue dysplasia was identified in 55.3% (n=63) of pregnant women with cervical insufficiency. Mild uCTD predominated, accounting for 74.6% of cases, while moderate and severe forms represented 25.4%. Patients in Groups II and III demonstrated significantly higher rates of early cervical shortening and pronounced funneling of the internal os compared with Group I. Biochemical analysis demonstrated an increased urinary excretion of hydroxyproline in pregnant women with uCTD, indicating enhanced collagen catabolism. At the same time, these patients showed reduced serum magnesium levels, including values within the lower borderline range. The incidence of preterm birth was higher among women with cervical insufficiency accompanied by uCTD, with the greatest risk observed in those with moderate to severe connective tissue dysplasia.

Pregnancy and Delivery Characteristics in Women with Cervical Insufficiency Associated with Connective Tissue Dysplasia

Pregnancy course and outcomes (Main group n=57; Comparison group n=28)

I left the structure exactly the same: cervical cerclage vs pessary in each group.

Translation of the table into English

Pregnancy course and outcomes

In dicator	Main group (n=57)		Comparison group (n=28)	
	Cerclage (n=24)	Pessary (n=33)	Cerclage (n=13)	Pessary (n=15)
	abs. %		abs. %	
Threatened miscarriage				
• in the 1st trimester	0 | 0	0 | 0	4 | 30.8±8.9*	7 | 46.7±9.6***
• in the 2nd trimester	7 | 29.2±9.5	11 | 33.3±8.3	6 | 46.2±9.6	8 | 53.3±9.6
• in the 3rd trimester	4 | 16.7±7.8	5 | 15.2±6.3	5 | 38.5±9.4*	5 | 33.3±9.1*
Suture tearing during uterine contractions				
• Yes	5 | 20.8±8.5	– | –	6 | 46.2±9.6*	– | –
Spontaneous miscarriage	2 | 6.1±4.2	1 | 4.2±4.2	2 | 15.4±6.9	2 | 13.3±6.5
Preeclampsia	2 | 8.3±5.8	2 | 6.1±4.2	2 | 15.4±6.9	2 | 13.3±6.5
Placental dysfunction	3 | 12.5±6.9	3 | 9.1±5.1	3 | 23.1±8.1	3 | 20.0±7.7
PPROM (preterm premature rupture of membranes)	5 | 20.8±8.5	4 | 12.1±5.8	6 | 46.2±9.6*	5 | 33.3±9.1
Chorioamnionitis	1 | 4.2±4.2	– | –	1 | 7.7±5.1	2 | 13.3±6.5
Term delivery	21 | 87.5±6.9	28 | 84.8±6.3	8 | 61.5±9.4*	10 | 66.7±9.1
Preterm birth	2 | 8.3±5.8	3 | 9.1±5.1	3 | 23.1±8.1	3 | 20.0±7.7
• at 22–27 weeks	– | –	– | –	1 | 7.6±5.1	– | –
• at 28–33 weeks	1 | 4.2±4.2	1 | 3.0±3.0	2 | 15.4±6.9	2 | 13.3±6.5
• at 34–37 weeks	1 | 4.2±4.2	2 | 6.1±4.2	– | –	1 | 6.7±4.8
Fetal loss	1 | 4.2±4.2	2 | 6.1±4.2	2 | 15.4±6.9	3 | 20.0±7.7

Note: * differences compared to the main group are statistically significant (*p<0.05, ***p<0.001)

Discussion

The findings obtained in this study confirm the systemic nature of cervical insufficiency in a substantial proportion of pregnant women. Disturbances in collagen metabolism and magnesium deficiency in the setting of uCTD lead to reduced strength of the cervical connective tissue framework and to its premature remodeling. Under these conditions, standard methods of preventing and managing cervical insufficiency, which are

primarily aimed at local mechanical support, often prove insufficiently effective. The demonstrated association between biochemical markers of connective tissue metabolism and the clinical manifestations of cervical insufficiency emphasizes the need for a comprehensive approach to predicting preterm birth, taking into account the systemic status of connective tissue.

Conclusion

Undifferentiated connective tissue dysplasia is a significant pathogenetic factor in the development of cervical insufficiency and preterm birth. A comprehensive assessment of clinical and biochemical markers of uCTD in pregnant women with cervical insufficiency makes it possible to identify a high-risk group and to justify an individualized approach to pregnancy management.

References

1. Nicholls-Dempsey L, Spiegel E, Czuzoj-Shulman N, Abenhaim HA. 574: Pregnancy outcomes in women with Ehlers-Danlos syndrome. Am J Obstet Gynecol. 2019; 220:1:381-382.

2. Norton PA, Allen-Brady K, Cannon-Albright LA. The familiarity of pelvic organ prolapse in the Utah population database. Int Urogynecol J. 2013; 24:3:413-418.

3. Oxlund BS, Ortoft G, Brüel A, Danielsen CC, Oxlund H, Uldbjerg N. Cervical collagen and biomechanical strength in non-pregnant women with a history of cervical insufficiency. Reprod Biol Endocrinol. 2018; 8:1:92.

4. Park JC, Kim DJ, Kwak-Kim J. Upregulated amniotic fluid cytokines and chemokines in emergency cerclage with protruding membranes. Am J Reprod Immunol. 2015; 66:310-319.

5. Petersen LK, Uldbjerg N. Cervical collagen in non-pregnant women with previous cervical incompetence. Eur J Obstet Gynecol Reprod Biol. 2019; 67:1:41-45.

6. Rafael T.J., Berghella V., Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. // Cochrane Database Syst Rev. - 2014. - Is. 9. - CD009166.).

7. Rafael T.J., Mackeen A.D., Berghella V. The effect of 17a-hydroxyprogesterone caproate on preterm birth in women with an ultrasound-indicated cerclage. Am J Perinatol. 2016; 28:389.

8. Ramírez-Bello J, Jiménez-Morales M, Functional implications of single nucleotide polymorphisms (SNPs) in protein-coding and non-coding RNA genes in multifactorial diseases. Gac Médica México. 2017; 153:2:238-250.

9. Romero R, Velez Edwards DR, Kusanovic JP. Identification of fetal and maternal single nucleotide polymorphisms in candidate genes that predispose to spontaneous preterm labor with intact membranes. // Am J Obstet Gynecol. 2014; 202:5:431.e1-431.e34.

10. Schlembach D, Maul H, Fittkow C, Olson G, Saade G, Garfield R. Cross-linked collagen in the cervix of pregnant women with cervical insufficiency. Am J Obstet Gynecol. 2013; 189:6:S70.