

# The Importance of Ultrasound Monitoring of the Normal and Lesional Cervical Ectropion Treatment

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**ABSTRACT:** Objective: to investigate the importance of various ultrasound prognosis features in the assessment of the cervical ectropion treatment monitoring. Method: The inclusion criteria was the presence of ectropion and the selection was based on clinical examination performed during routine consultations in specialized clinics, later confirmed by colposcopic evaluation of cervix. The evaluation protocol included: clinical evaluation completed with colposcopy, guided biopsy when lesions were suspected, serological assay of day 21 progesteronemia, presence of Chlamydia, Mycoplasma, Ureaplasma, HVS type II, HPV and bacterial infections, transvaginal ultrasound serial evaluation at the 7th, 14th and 21st day before and after treatment concerning: cervical volumetric calculations and velocimetric measurements of uterine arteries flows. Progestative treatment was prescribed, and anti-infectious specific treatment when needed. Patients were reevaluated after 3 months. Results: The prospective study included 45 patients between 2013-2014. 28 presented serum progesterone levels below the reference range or borderline. We noted a moderate reduction of the ectropion area in 42 % and a marked reduction in 58% of the cases. No statistically significant differences were found between the size of the cervix before or after treatment, except certain evaluations (the 7th and the 14th day) in the presence of bacterial coinfections. Evaluation of pulsed Doppler velocimetric indices of uterine arteries flows showed generally minor variations with no constant positive or negative trend. Conclusion: Based on the data obtained in our study, we conclude that ultrasound monitoring of ectropion treatment do not provide reliable prognosis data regarding the evolution of cervical lesion.

**KEYWORDS :** ectropion, ultrasound, colposcopy, cervical volume

## Introduction

Cervical cancer worldwide has the third leading incidence of all malignancies in women, ranking in the top five diseases causing mortality [4,10,14,16]. The incidence in Europe is 13.4 per 100,000 women and in our country 34.9 cases per 100,000 women [5,6,38-40]. Romania has the highest incidence of cancer mortality in the age group 15-44 years in Europe. [34,35,37]

It is well known that cervical ectropion is a cervical lesion with oncogenic risk, but the studies are still inconsistent on solving this type of injuries [21,24,26,29,31]. What is more, nowadays the 14-37% reported incidence for cervical ectropion is increasing. [23,25,27,30] Also, additional diagnosis of Chlamydia, Mycoplasma, Ureaplasma, HPV, HVS2, places the patient into a group of greater oncogenic risk. [1-3,8,13]

Antimicrobial- hormonal combined therapy is an important tool to manage such cases with potential dysplastic oncogenic impact [7,9,11,12]. Progesterone administered intermittently during ovulatory to luteal phase, between days 10-14, with varying doses

depending on serologically proven deficiency in patients with premenstrual syndrome presenting cervical lesions of the cervix, leads to the induction of transformation zone restriction with re-epithelization in the squamous epithelium [15,30,32,36].

However, there is scarce data in the literature regarding the cervical ultrasound imaging using volumetric, linear and Doppler ultrasound (measurement of uterine artery resistance indices) and prompted our study into this segment. [17,18,22,33]

## Aim

We chose to conduct a sonographic study in patients diagnosed and treated for congenital ectropion to investigate the importance of various ultrasound prognosis features, in order to create an effective algorithm for treatment monitoring.

## Methods

During the study period, patients were admitted into the study group after signing an informed consent. Then they were subject to an

investigation protocol aimed to investigate the prognosis potential of several measurable cervical parameters that can be used for monitoring the cervical ectropion treatment (Fig.1).

Inclusion criteria was the presence of ectropion and the selection was based on clinical

examination performed during routine consultations in specialized clinics, later confirmed by colposcopic evaluation of cervix.

Demographic data recorded in the patients were: age, origin, characteristics of the menstrual cycle, comorbidities, history of personal or familial cervical pathology.

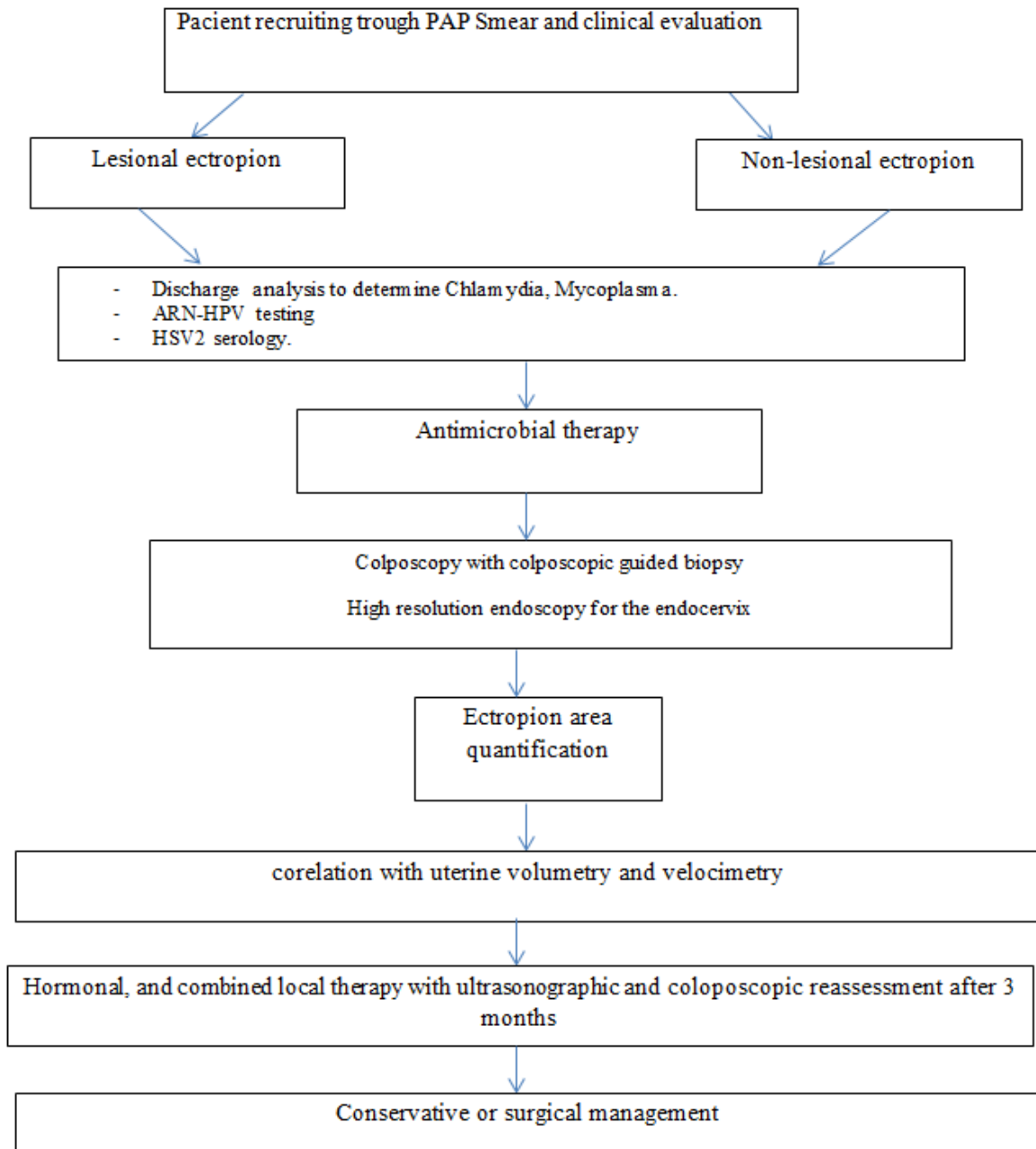


Fig.1. Protocol diagram

**Evaluation protocol for the studied patients included:**

A. Clinical general and local evaluation, completed with colposcopy+/- colposcopic guided biopsy.

B. Serology Assay: day 21 progesteronemy (to determine the hormonal context for ectropion evolution); IgM and IgG HVS2; Atg Chlamydia, Mycoplasma and Ureaplasma, HPV DNA typing; vaginal bacteriology.

C. Transvaginal ultrasound serial evaluation at the 7th, 14th, 21st day concerning: uterine and cervical volumetric calculations and velocimetric measurements of uterine arteries flows. We used Voluson E6 ultrasound equipment from General Electrics.

After determining the ectropion diagnosis and area, the serologic progesterone level and the infectious context, progestative treatment was prescribed hormone, and antiinfectious specific treatment when needed, with reassessment after 3 months.

Antibiotic protocol was standard with tetracycline, macrolides and quinolones whose efficiency was investigated at 3 months reevaluation. Antiviral therapy was initiated using Isoprinosine for HPV and valacyclovir for HVS2.

**Statistical analysis of data**

For data processing we used IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, NY, USA).

For data normality tests we used Shapiro-Wilks and Kolmogorov-Smirnov.

To study the evolution of volumes, IR and ectropion level under therapy, in case of normal distribution of data we used Paired – samples T test and Wilcoxon Signed Rank validity test for data that did not have normal distribution.

Patients were studied as a global group, but also as separate subgroups divided according to different variables.

For data analysis we used frequency tables which included two columns: one for distinct values of the variable analyzed, and the other for frequencies of those values.

Descriptive statistics (mean and standard deviation or median with minimum and maximum value) was used for the presentation of the basic characteristics.

**Results**

The prospective study included 45 patients between 2013-2014.

**Table 1. Associated infections in the studied group**

Infection	Number of cases	%
Atg Chlamydia	4	8.9
Mycoplasma	4	8.9
Ureaplasma	12	26.7

**Associated microbial infections**

Out of 45 patients, we identified Chlamydia infection in 4 patients, mycoplasma in 12 patients and ureaplasma in 4 patients (Table 1).

**Hormonal profile of patients with ectropion**

Patients were divided into 2 subgroups: 28 presented serum progesterone levels below the reference range or borderline reduced and 17 patients had serological values of progesterone in the normal reference interval.

**Colposcopic guided biopsy results**

Histopathological study with HE staining, of the 45 cases revealed a number of changes in the area of ectropion. Please note that in some cases, were identified two or more microscopic changes described below. Microscopic changes observed with usual staining in ectropion areas were grouped as follows (Table 2):

**Table 2. Histopatological findings with HE stain**

Histopatological findings	N	%
Nonspecific inflamatory tissue	16	35.6
Koylocites	16	35.6
Metaplasia imature	5	11.1
Metaplasia mature	15	33.3
Displasya medium	2	4.4
Displasya mild	9	20.0
Acanthosis	7	15.6
Acanthosis, papillomatosis	4	8.9
Acanthosis, papillomatosis, parakeratosis	2	4.4
Parakeratosis	1	2.2
Parakeratosis, acanthosis	4	8.9
Intraepithelial vesicle	1	2.2

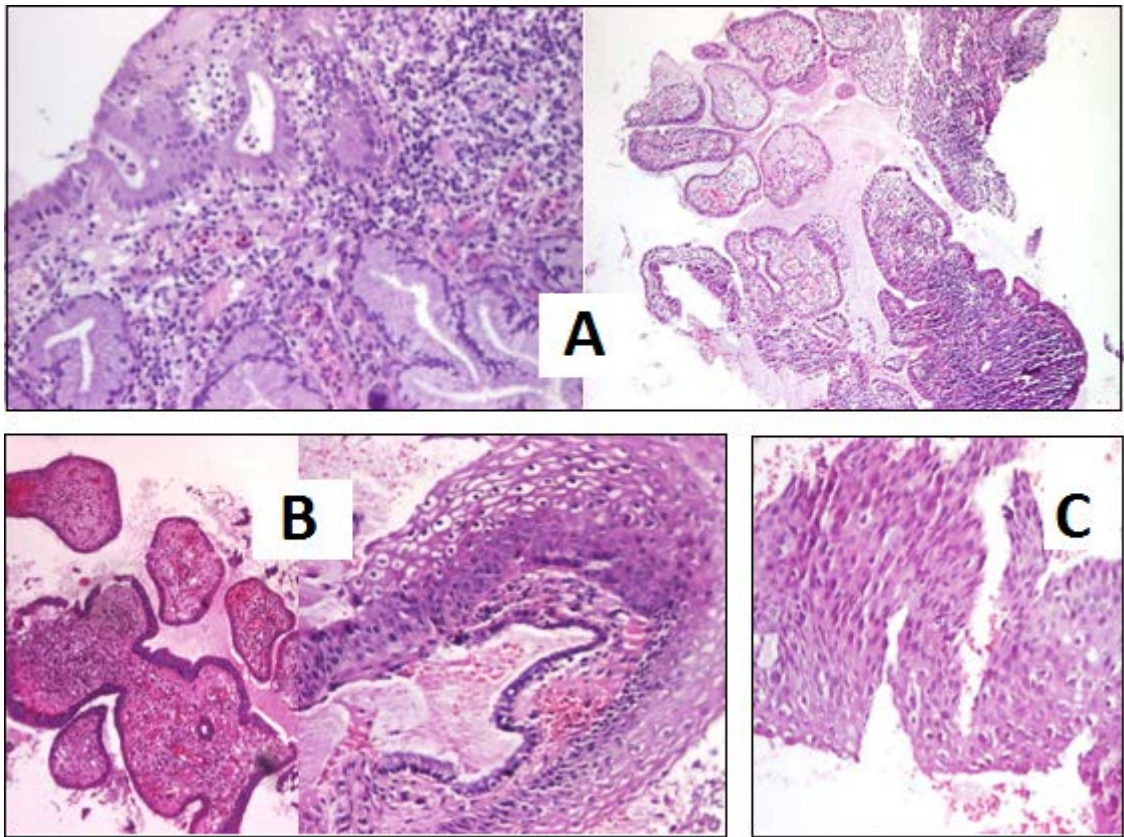
**Systemic and local hormonal treatment**

The 50 patients were prescribed with different treatment schedules based on particular benefit for each case. 5 patients were excluded from statistical analysis because they did not accept any hormonal treatment.

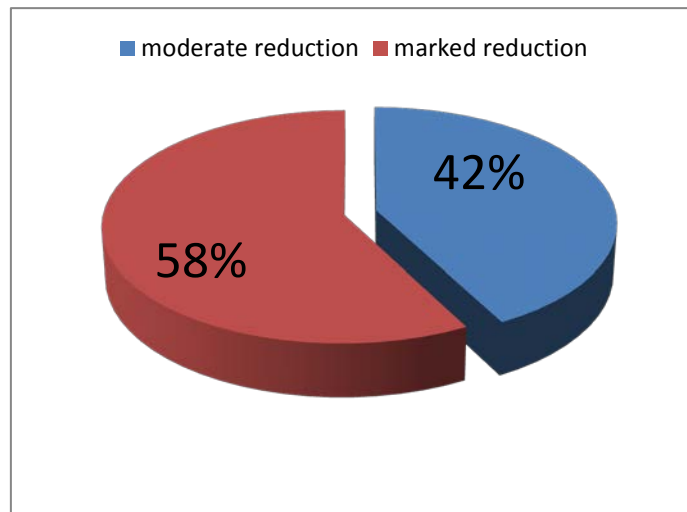
In the studied cases semi-synthetic progestogen therapy was indicated in the luteal phase (nomegestrol acetate 5 mg/day or 10-20 mg dydrogesterone/day) or derivatives of natural micronized progesterone.

**Colposcopic evaluation after treatment**

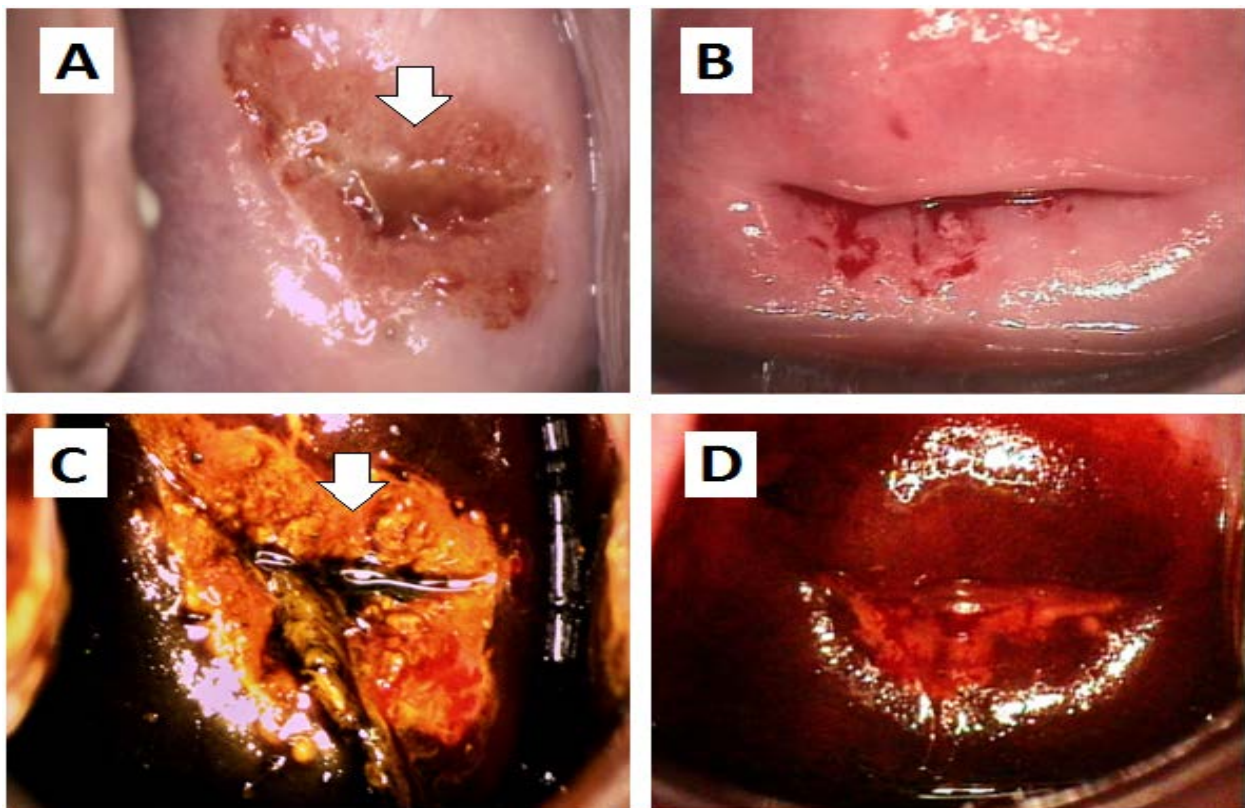
We noted a moderate reduction of the ectropion area in 19 cases (aproximately 42 % ) and a marked reduction in 26 cases (58%).



**Fig.2. A:** Ciliar tubal metaplasia and plasmocytes cervicitis associated with ectropion and chronic inflammatory infiltrate in the corium prone to formation of lymphoid follicles, col. HE. **B:** Micropolyps aspect of ectropion area, vascular ectasia, inflammatory infiltrate and LSIL (CIN I) on squamous metaplasia, col.HE. **C:** HSIL on squamous metaplasia area, col. HE.



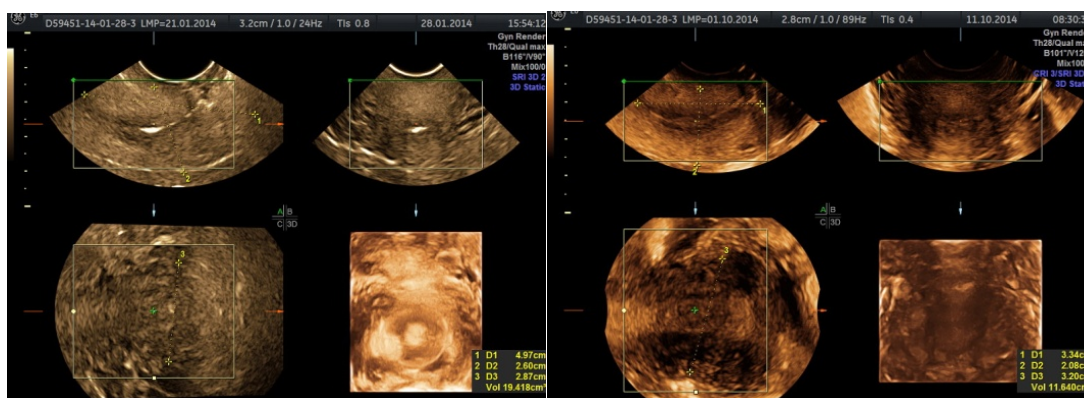
**Fig.3. Ectropion severity regression.**



**Fig.4. Colposcopy in HPV negative patient with ectropion (marked with arrow), before (A, C) and after treatment (B, D). A: acetic acid staining of the cervix, before treatment. B: ectropion remission after six months, acid acetic application. C: ectropion extent evaluated using Lugol's stain. D: ectropion remission after six months, same patient, iodine staining.**

### Ultrasonographic study results

Cervical volumetry interrelated with menstrual cycle phases (Fig.5)



**Fig 5. 3D ultrasound of the cervix. Patients with Chlamydia, on 7th day of MC before treatment (volume 19,418 cm<sup>3</sup>) and 7th day of MC after treatment (volume 11 640cm<sup>3</sup>)**

No other statistically significant differences were found between the size of the cervix before or after treatment, than differences in absolute value. Cervical volumes were reduced in certain

evaluations (for example the 7th and the 14th day) in the presence of bacterial coinfections (Table 3).

**Table 3. Cervical volumes in the presence of coinfections ( Data are expressed as average +/-SD; P < 0.05 – statistically significant – T pair test)\*. CB: cervical biopsy.**

		Before treatment		After treatment		t	p value
		Average	SD	Average	SD		
<b>Cervical volume day 7</b>	Chlamydia +	20.058	6.216	22.747	5.870	-7.040	0.006
	Ureaplasma +	24.156	7.350	21.161	5.582	3.165	0.009
<b>Cervical volume day 14</b>	Chlamydia -	24.604	7.230	23.037	5.202	2.097	0.042
	Ureaplasma +	26.693	7.217	23.085	5.770	2.504	0.029
	HPV HR	28.566	8.542	23.705	6.944	2.686	0.036
	Nonspecific inflammatory tissue(CB)*	25.260	7.278	22.663	5.636	2.198	0.044

After hormonall treatment, followed by the reduction of the ectropion, there were no statistically significant differences in the volumetric measurements of the cervix.(Table 4).

**Table 4. Cervical volume after progesterative treatment ( Data are expressed as average +/-SD; P < 0.05 – statistically significant – T pair test)**

	Before treatment	After treatment	t	p
	Average+/-SD	Average+/-SD		
<b>Cervical volume day 7</b>	22.21 ± 7.06	22.12 ± 6.33	0.143	0.887
<b>Cervical volume day 14</b>	24.12 ± 7.31	22.83 ± 5.1	1.826	0.075
<b>Cervical volume day 21</b>	23.23 ± 6.67	23.33 ± 5.73	-0.164	0.871

Imagistic reduction of the cervix volume after treatment was statistically significant for day 7 in patients with positive Clamydia and Ureaplasma.

Cervical volume reduction measured on day 14 of the menstrual cycle, was statistically significant for patients HPV HR+, correlated

with low progesterone serologic values. Also, in the same high statistical significance interval, entered patients who experienced frequent menstrual cycles (days 21-25) and in a lesser extent, patients with non specific inflammatory histopathological result.

#### Evaluation of uterine artery velocimetry

**Table 5. Variation in resistance indices after treatment for uterine arteries for the entire lot of patients. Data are expressed as average +/-SD in case of normal distribution, or as median in case of abnormal distribution. P < 0.05 – statistically significant ( T pair test for normal distribution data and Wilcoxon Signed Rank test for abnormal distribution data)**

	Right UAday 7		Right UAday 14		Right UAday 21	
	N	%	N	%	N	%
>(-50%)	0	0	0	0	1	2.2
(-50%)-(-25%)	0	0	0	0	0	0
(-25%)–0	29	64.4	30	66.7	17	37.8
0-25%	16	35.6	15	33.3	27	60.0
25%-50%	0	0	0	0	0	0
>50%	0	0	0	0	0	0

% RI reduction	Left UA day 7		Left UA day 14		Left UA day21	
	N	%	N	%	N	%
>(-50%)	0	0	0	0	0	0
(-50%) - (-25%)	0	0	0	0	0	0
(-25%) – 0	27	60.0	15	33.3	30	66.7
0-25%	18	40.0	30	66.7	15	33.3
25%-50%	0	0	0	0	0	0
>50%	0	0	0	0	0	0

## Discussion

This study confirms previous research that induction of luteal phase progestogen hormone treatment induces the decrease of ectropion extension, that further may lead to the decrease of the transformation zone and spontaneous negativation of viral infection and involution of cervical lesions.

No statistically significant differences were noted in the overall cervical volumetric measurement after treatment was administered. However, measurements taken on day 7 and day 21 in patients infected with chlamydia, showed a significant decrease in the cervical volume after treatment and especially after treatment with cephalosporin, but the result should be validated in a larger study. This could suggest a reduction in cervical volume by decreasing inflammation, since hormonal therapy was not significantly involved as an independent variable. The variation of the cervical volume was significant but less notable in the cases of ureaplasma and mycoplasma infections.

Evaluation of pulsed Doppler velocimetric indices of uterine arteries flows showed absolute variations but the vast majority were minor, up to 25% from the initial findings. We could not identify a constant positive or negative trend, in any of the uterine arteries, during the menstrual cycle, and also the indices varied widely as amplitude. Note that these indexes have suffered the most significant changes in the periovulatory phase at the left uterine artery towards lower values, but later in the day 21, in the end of treatment, the respective indices were increased compared to previous values. Moreover, this trend has not been followed by the measurements in the contralateral uterine artery. Since changes were inconstant and minor, we conclude that uterine vasculature was not influenced by the treatment or remission of the cervical ectropion. An issue that requires further investigation with possible prognostic implication is that the changes in resistance

uterine arteries index was higher in patients without Chlamydia infection and positive for HPV-HR infection and patients with low progesteronemy. It might be true the hypothesis that progesterone therapy is more effective if the ectropion is "clean" bacteriological and viral, but this assumption requires confirmation by further research with similar therapeutic protocol. Based on the data obtained in our study, we conclude that ultrasound monitoring of ectropion treatment do not provide reliable prognosis data regarding the evolution of cervical lesion.

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## References

1. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. No 45, August 2003. Cervical cytology screening. *Obstet Gynecol* 2003;102:417;
2. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. No 61, April 2005. Human Papillomavirus. *Obstet Gynecol* 2005; 105:905;
3. Anton AC, Peltecu G. Leziunile precursorare ale cancerului de col uterin. In: Irinel Popescu, editor. *Tratat de chirurgie, vol. V A*, editor Peltecu G, editura Academiei Române, București 2008;
4. Barbara S. Apgar, Gregory L. Brotzman, Mark Spitzer. *Colposcopy. Principles and Practice*. Second Edition. 149-175. 2008;
5. Belfiore P, Costa E, De Cantis S, et al. Effectiveness and persistence of a topical treatment for cervical ectropion with deoxyribonucleic acid. *Minerva Ginecol* 2005; 57-461.;
6. Benacerraf BR, Shipp TD, Bromley B. Improving the efficiency of gynecologic sonography with 3-dimensional volumes. *J Ultrasound Med* 2006; 25:165;

7. Benevolo, M. , M. Mottolese , and F. Marandino . et al. Immunohistochemical expression of p16(INK4a) is predictive of HR-HPV infection in cervical low-grade lesions. *Mod Pathol* 2006. 19:384–391;
8. Berek JS. Berek & Novak's Gynecology, Thirteenth Ed. Benign Diseases of the female reproductive tract. Pag 438, lippincott, Philadelphia, 2002;
9. Bergonzini, V., Salata, C., Calistri, A., Parolin, C. & Palu, G. 2010. View and review on viral oncology research. *Infectious Agents and Cancer*, Vol.5;
10. Bosch, F.X., Lorincz, A., Munoz, N., Meijer, C.J. & Shah, K.V. 2002. The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology*, Vol.55;
11. Bucur Gh, Giurcăneanu C, Bucur L – Implicațiile infecțiilor venerice în patologia generală, Edit. Celsius, Buc., 2002;
12. Cantor SB, Cárdenas-Turanzas M, Cox DD, et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstet Gynecol* 2008; 111:7.
13. Coelho F.R.G., Prado J.C.M., Pereira Sobrinho J.S, Hamada G., et al Estrogen and progesterone receptors in human papilloma virus-related cervical neoplasia, *Braz J Med Biol Res*, Volume 37(1), 83-88, 2004;
14. Casey, P. M., Long, M. E., & Marnach, M. L. 2011, February. Abnormal cervical appearance: what to do, when to worry?. In *Mayo Clinic Proceedings* Vol. 86, No. 2, pp. 147-151. Elsevier;
15. Castellsague X, Diaz M et al. Worldwide HPV etiology of cervical adenocarcinoma and its cofactors: implication for screening and prevention. *J Natl Cancer Inst* 2006; 98:303;
16. Chung S-H, Franceschi S, Lambert PF. Estrogen and ERα: Culprits in Cervical Cancer. *Trends in endocrinology and metabolism*: TEM 2010;21(8):504-511. doi:10.1016/j.tem.2010.03.005;
17. Clifford G, Franceschi S. *Int J Cancer* 2008; 122, 1684-5;
18. Cuzick J, Clavel C et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* 2006; 119:1095;
19. Dallenbach-Hellweg G, Knebel Doeberitz MV, Trunk MJ, Normal histology, regeneration and repair, in *Color atlas of histopathology of the cervix uterin*, 13-29, second edition, Springer Verlag Berlin, 2006;
20. Davey DD et al Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med* 2004;128: 1224-1229;
21. Denny, L., Kuhn, L., Pollack, A., Wainwright, H., & Wright, T.C. Jr. 2000 Evaluation of alternative methods of cervical cancer screening for resource-poor settings. *Cancer*, 89, 826-33;
22. Dabbs DJ *Immunohistology of the female genital tract in Diagnostic immunohistochemistry, Theranostic and genomic applications*, 4th Edition, Elsevier, 653-709, 2014;
23. De Vuyst H, Claeys P, Njiru S, Muchiri L, Steyaert S, De Sutter P, Van Marck E, Bwayo J, Temmerman M. Comparison of pap smear, visual inspection with acetic acid, human papillomavirus DNA-PCR testing and cervicography. *International Journal of Gynaecology and Obstetrics*, 2005 May, 89:120-6;
24. Eleutério J Jr, Giraldo PC, Gonçalves AK, Cavalcante DI, de Almeida Ferreira FV, Mesquita SM, et al. Prognostic markers of high-grade squamous intraepithelial lesions: The role of p16INK4a and high-risk human papillomavirus. *Acta Obstet Gynecol Scand* 2007;86:94-8;
25. Famularo G., Pieluigi M., Coccia R., Mastroiacovo P., DeSimone C. – Microbiology, bacterial vaginosis and probiotics: perspectives for bacteriotherapy, *Med Hypotheses* 2001; 56: 421-30;
26. Ferenczy A, Franco E. Persistent human papillomavirus infection and cervical neoplasia. *Lancet Oncol*.2002; 3:11–6;
27. Giraldo P, Cavalcante DM, Linhares IM, Pompeu MM, Eleuterio J, The utility of p16 INK4a and Ki-67 to identify high-grade squamous intraepithelial lesion in adolescents and young women, *Indian Journal of Pathology and Microbiology*, Volume: 55, Issue: 3, 339-342, 2012;
28. Gage JC, Hanson VW, Abbey K, et al. Number of cervical biopsies and sensitivity of colposcopy. *Obstet Gynecol* 2006; 108:264-72;
29. Green, J.A, Kirwan, J.M., Tierney, J.F, Symonds, P., Fresco, L., Collingwood, M., & Williams, C.J. 2001. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*, 358, 781-786;
30. Guido R, Schiffman M, Soloman D, Burke L. Postcolposcopy management strategies for patients referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous lesions of undetermined significance: a two-year prospective study. *Am J Obstet Gynecol* 2003;188:1401-5;
31. Huang Z, Zhu W, Meng Y: Novel rabbit monoclonal antibody to estrogen receptor (clone SP1): no heat pretreatment but effective on paraffin embedded tissue, *Appl Immunohistochem Mol Morphol* 13: 91-95, 2005;
32. Hu, L. , M. Guo , and Z. He . et al. Human papillomavirus genotyping and p16INK4a expression in cervical intraepithelial neoplasia of adolescents. *Mod Pathol* 2005. 18:267–273;
33. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007; 370:1609.;
34. Jeronimo J, Schiffman M. Colposcopy at a crossroads. *Am J Obstet Gynecol* 2006; 195:349-53;
35. Junior, J. E., Giraldo, P. C., Gonçalves, A. K. S., do Amaral, R. L. G. and Linhares, I. M. 2014, Uterine cervical ectopy during reproductive age: Cytological and microbiological findings. *Diagn. Cytopathol.*, 42: 401–404. doi: 10.1002/dc.23053;



36. López, Jacqueline et al. "Human Papillomavirus Infections and Cancer Stem Cells of Tumors from the Uterine Cervix." *The Open Virology Journal* 6, 2012: 232–240. PMC. Web. 3 Dec. 2014;
37. Machado Junior LC, Whitaker Dalmaso AS, de Carvalho HB. Evidence for benefits from treating cervical ectopy: literature review. *Sao Paulo Med J* 2008;
38. Martens, Jolise E., et al. "Distribution pattern and marker profile show two subpopulations of reserve cells in the endocervical canal." *International Journal of Gynecologic Pathology* 28.4 , 2009: 381-388;
39. Martens, Jolise E., et al. "Reserve cells in human uterine cervical epithelium are derived from Müllerian epithelium at midgestational age." *International Journal of Gynecologic Pathology* 26.4 , 2007: 463-468;
40. McIver, Christopher J. et al. "Multiplex PCR Testing Detection of Higher-Than-Expected Rates of Cervical Mycoplasma, Ureaplasma, and Trichomonas and Viral Agent Infections in Sexually Active Australian Women". *Journal of Clinical Microbiology* 47.5 , 2009: 1358–1363. PMC. Web. 3 Dec. 2014;
41. McCredie M, Sharples K, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study, *Lancet*, 2008, 9:425–34;

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