

# ORAL CANDIDOSIS PREVALENCE ON PATIENTS WITH PREMATURE OVARIAN INSUFFICIENCY

GABRIELA MIȚARIU<sup>1</sup>, MIHAELA STANCIU<sup>2</sup>, MIHAELA CIOCAN<sup>3</sup>

<sup>1,2</sup>„Lucian Blaga” University of Sibiu, <sup>3</sup> Clinical County Hospital of Tg. Mureș

**Keywords:** oral infection with *Candida*, precocious menopause

**Abstract:** The oral infection with *Candida* is opportunistic, the pathogen agent using the diminishing of the resistance of the organism, in order to become consensual, pathogen. Starting from the premises that the secretion rhythm of the saliva and the salivary pH depend on the concentration of the circulating estrogen, we intended to research on the risk factors favoring the development of the oral candidosis on women with hyper-estrogenism. So we analyzed the quantity of saliva after the stimulation, as well as the salivary pH on a 53 patients group with precocious ovary insufficiency, compared with a testimony group of 50 healthy women. The patients with precocious ovarian insufficiency had an un-stimulated salivary flux inferior to the one of the testimony group and a lower salivary pH. The oral candidosis confirmed on the Sabouraud culture was present on 13,2 % from the patients with precocious ovarian insufficiency and on 2% of the women from the testimony group, with a positive correlation ( $p=0,024$ ) between the presence of the oral candidosis and the premature ovarian insufficiency. It can be mentioned, with a 99% certainty ( $p=0,000$ ), the presence of the positive correlation between the premature ovarian insufficiency and the oral candidosis prevalence. The conclusion of the research: the oral health of the patients with precocious menopause is altered by hypo-estrogenism that attracts the hypotrophy of the oral mucosa, diminishing the salivary pH and the salivary flux and structurally and functionally modifying the pathologic reproduction of the species of *Candida* in the oral cavity.

**Cuvinte cheie:** candidoză orală, insuficiență ovariană prematură

**Rezumat:** Infecția orală cu *Candida* este una oportunistă, agentul patogen folosindu-se de diminuarea rezistenței organismului pentru a deveni din comensual, patogen. Plecând de la premiza că ritmul de secreție al salivei și pH-ul salivar depind și de concentrația estrogenilor circulanți, ne-am propus să cercetăm factorii de risc care favorizează dezvoltarea candidozei orale la femeile suferinde de hipostrogenism. În acest sens am analizat cantitatea de salivă bazal și după stimulare, precum și pH-ul salivar la un lot 53 de paciente cu insuficiență ovariană precoce, comparativ cu un lot martor de 50 femei sănătoase. Pacientele cu insuficiență ovariană precoce au avut un flux salivar nestimulat inferior femeilor din lotul martor și un pH salivar în salivă mai scăzut. Candidoza orală confirmată pe mediul de cultură Sabouraud a fost prezentă la 13,2% din pacientele cu insuficiență ovariană precoce și la 2% la femeile din lotul martor, existând o corelație pozitivă ( $p=0,024$ ) între prezența candidozei orale și insuficiența ovariană prematură. Se poate afirma cu o încredință de 99% ( $p=0,000$ ) prezența corelației pozitive între insuficiența ovariană prematură și prevalența candidozei orale. Concluzia cercetării: sănătatea orală a pacientelor cu menopauză precoce este alterată de hipostrogenism, condiție care antrenează hipotrofia mucoasei orale, diminuează pH-ul salivar și fluxul salivar, modificări structurale și funcționale favorabile înmulțirii patologice a speciilor de *Candida* în cavitatea orală.

## INTRODUCTION

The premature ovarian insufficiency is defined as amenorrhea with more than 4 month duration, before 40, with high levels of gonadotrofine, mainly FSH (over 40UI/l). The affection is also called precocious menopause and recognizes many ethologies: iatrogenic, self-immune, genetic, toxic (1). The monitoring of the patients with premature ovarian insufficiency aims at the avoidance of the complications due to hypostrogenism, as the cardio-vascular diseases, the osteoporosis, the atrophy of the genital tract (2).

Through techniques of immune-histochemistry receptors for estrogen hormones have been emphasized (3). The estrogens maintain the trophicity of the normal functions of the mucosa of the oral cavity and so the balance of the micro-organisms from the oral cavity. The salivary secretion as well as the salivary pH is correlated with the level of the circulating

estrogens (4). It was found out that hypo – estrogenism produces glosodinie, xerostomie and diminishes the sensitivity over the bitter taste at 40% from the women at menopause. Another cause, besides the lowering of the circulating estrogens that produces the sensation of burning at the level of the tongue is candidosis (5). At 40 – 60% from the healthy women, different species of *Candida* can be emphasized inside the buccal cavity, the levura being a part of the normal flora of the mouth (6,7)

## PURPOSE OF THE STUDY

Starting from the fact that the rhythm of secretion of the saliva and the salivary pH depend also on the concentration of the circulating estrogens, we intend to research on the factors of risk that favor the development of the oral candidosis on women with hypo – estrogenism. So, we analyzed the quantity of basal saliva after stimulation, too, as well as the salivary pH on a

<sup>1</sup>Corresponding Author: Gabriela Mițariu, Medicine Faculty “Victor Papilian”, 2A Lucian Blaga street, Sibiu, 550169, România; e-mail: gabimitaru@yahoo.com

Article received on 03.05.2010 and accepted for publication on 18.05.2010  
ACTA MEDICA TRANSILVANICA September 2010; 2(3) 203-206

## CLINICAL ASPECTS

group of women affected by the precocious ovarian insufficiency.

Another objective of the study is the research of the prevalence of oral candidosis on women with precocious menopause, compared to women with normal ovarian activity.

The third objective was to elaborate a practical guide for the patients with precocious menopause, as well as for the doctor, in order to prevent and heal the oral manifestations caused by hypo-estrogenism.

### MATERIAL AND METHOD

The study was done during the period 2006-2008. it was a transversal research in two sanitary units (the Clinic of Endocrinology and the Ambulatory of Stomatology from Sibiu).

The group was of 53 patients with premature ovarian insufficiency.

The patients were asked to fill in a form concerning the moment of amenorrhea and the oral subjective and objective symptoms (sensation of dry mouth, burnings on the tongue, taste modifications, loaded tongue, creamy deposits on the intern face of the cheeks).

The diagnosis of precocious ovary insufficiency was put after the anamnesis, the clinic exam and the hormone dosage. The oral candidosis diagnosis was represented by the finding of the pseudohife on the wet froitiu, with confirmation in the Sabouraud culture. The prelevations for the froitiu were done at the level of the oral mucosa. More profound and suspect lesions maybe produced by Candida have been examined histologically on the tests obtained through biopsy.

There have been collected basal saliva tests (without stimulation) and after stimulation in GC Salivar Check Buffer testers. The salivary flux (degree of hydration of the saliva) and the pH of salivary break. The stimulated salivary flux was determined after stimulation through 30 minutes mastication of a cube of sterile paraffine from the kit. The pH was determined by pouring one drop of saliva on the paper band of the pH kit and the comparing after 2 minutes of the color with the one of the reference set.

### RESULTS

The research analyzed the testimony group of 50 healthy women, with present menstrual cycles, aged between 37+-8,32 and 53 patients suffering from premature ovarian insufficiency, with the following characteristics (Tab.nr.1).

**Table no. 1. Representing the characteristics of patients with early ovarian failure**

	Precocious ovarian insufficiency	Testimony group	P Likelihood ratio
Average age	36 ± 6,40 ani	37±8,32 ani	
Buccal accuses	17(32,07%)	3(6,0%)	
Un-stimulated salivary flux	0,32±0, 0,06 ml/min.	0,39±0, 0,04 ml/min	p=0,000
Salivary flux after stimulation	1,3±0,09 ml/min	1,7±0,05 ml/min	
Salivary pH	6,7±0,8	7,1±0,9	p=0,000
Suspected, at clinical exam, of oral candidosis	9(16,98%).	2(4%)	
Candida present inside the oral cavity	31(58,49%).	17(34,0%)	p=0,012
Oral candidosis confirmed on Sabouraud culture environment	7(13,20%)	1(2,0%)	p=0,04

### DISCUSSIONS

The total number of patients with premature ovarian insufficiency in study was of 53 with an average age of 36±6,40.

The ethylogy of the premature ovarian insufficiency was the ovariectomy: 31 (58,49%), self-immune: 13 (21,52%) and Turner syndrome: 9 (16,98%).

The patients with precocious ovarian insufficiency presented buccal accuses: in 32% of the cases compared with 6% of healthy women.

After the statistic analysis a conclusion could be drawn with a 99% precision (p=0,000), that there is a significant statistic difference between the salivary flux of the patients with premature ovarian insufficiency, compared with the women from the testimony group. Thus, the level of the salivary flux was lower at the patients with ovarian insufficiency (0,32 – un-stimulated; 1,30 – stimulated), compared to the testimony group (0,39 – un-stimulated; 1,70 – stimulated).

As for the salivary pH a conclusion can be drawn with a 99% precision (p=0,000), that there was a significant statistic difference between the level of the salivary pH in the stimulated saliva of the patients with premature ovarian insufficiency from the testimony group. Thus, the level of the salivary pH in the stimulated saliva is lower at those with ovarian insufficiency (6,7), compared to the women of the testimony group (7,1).

At the patients with clinic precocious ovarian insufficiency, the diagnosis of buccal candidosis was suspected on 9 (16,98%) while only 2(4%). women of the clinic testimony group were suspected of buccal candidosis .

The patients with precocious ovarian insufficiency had Candida in the buccal cavity in 31 (58,49%) of the cases, while Candida was found in the buccal cavity only at 17(34%) of the women from the testimony group. It comes out that the premature ovarian insufficiency represents a factor of risk for the oral candidosis (the relative risk was of 1,72%).

At the patients with precocious ovarian insufficiency the oral candidosis was confirmed on the Sabouraud culture for 7 (13,20%), while the testimony group confirmed it on only one person.

The estrogens are confirmed in the modulation of the cells growth, the differentiation and the regulation of the reproduction function. The steroid sexual hormones seem to play a significant role in the physiology of the oral cavity. They modulate the maturation of the epithelial cells, including those from the buccal mucosa (8).

The lowering of the estrogens during menopause affects the process of maturation of the buccal epithelia, leading to its weakening. The atrophied epithelia lead to different infections, including the fungi ones (9,10).

A series of studies showed that the therapy of hormone substitution prevents these things at post- menopause women, suggesting the role of the feminine sexual hormones for the maintenance of the troficate of the buccal mucosa. (11,12). The salivary secretion is regulated by many hormones among which the estrogens play a very special role. During the menstrual cycle, the pregnancy and the menopause, the composition of the saliva pH is modified.

The estrogens contribute at the maintenance of the acid-basic balance in the buccal cavity through many mechanisms. Normally the mouth is easily acid.

Candida, on some researchers, blocks the estrogen receptors from the buccal mucosa; as a result, it can be said that the presence of candida in high quantity in the oral cavity can produce local estrogenism, inducing a sensitivity of the receptors to estrogens. The blocking of the estrogen receptors can lead to the relative domination of the progesterone and the testosterone that raise the risk of hypoestrogenism (13).

The substitution treatment with estrogen raises the neutralizing effect of the saliva (raises the pH) and also raises the salivary secretive debit (14).

The cited studies suggest that the estrogens play an

## CLINICAL ASPECTS

important role in maintaining the trofocitate of the buccal mucosa and of the salivary glands. After menopause, the salivary flux diminishes (15, 16, 17, 18).

Turner syndrome associates with intense signs and symptoms of hypostrogenism (19, 20). Oral candidosis often associates with the angular cheilitis (Fig.nr.2).

**Figure. no. 1. A. The patient AV, 32 years old, Turner syndrome**



**Figure no. 1. B. Ogival palate, pterygium colli, low insertion of scalp. Dg. Erytemateous chronic oral candidosis**



The intimate mechanisms through which the estrogen lack influences the oral manifestations favoring the development of Candidosis in the oral cavity are not known, but the reduction of the number of estrogen receptors in the buccal mucosa and in the salivary glands could be a first cause. The histological aspect of the oral mucosa is similar to the vaginal mucosa. The vitality dependency of the vaginal mucosa on estrogen is already proved, the atrophic modifications due to am estrogen lack could be extrapolated on the oral mucosa. In a precocious menopause the raised prevalence of the oral candidosis could be due to hypo estrogen, pH lowering of the salivary flux (Fig.3).

The estrogen substitution treatment in precocious ovarian insufficiency could prevent and heal the oral manifestations of this patient. For that we need random clinical studies, controlled on long term, in order to prove the benefits of the estrogen substitution treatment on the oral discomfort at precocious menopause (21,22).

**Figure no. 2. Angular cheilitis**



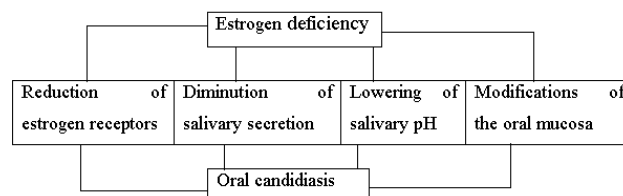
Angular cheilitis (fig.2) was the most frequent form of oral candidosis at the patients with precocious menopause and those with Turner syndrome.

The hyperplasic chronic candidosis was present at a patient with precocious menopause. It can be taken for

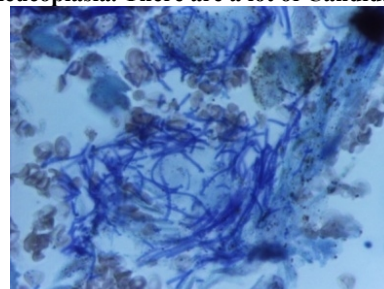
leucoplakia (white persistent spots on the cheeks and tongue). Leucoplakia is a pre-cancer state. (23).

For a differential diagnosis in such a situation a biopsy for differential diagnosis was needed. (fig.4)

**Figure no. 3. Mechanisms involved in the pathogenesis of the oral candidosis in precocious menopause**



**Figure no. 4. Biopsy on the buccal mucosa in a patient suspect of leucoplakia. There are a lot of Candida pseudihife**



### CONCLUSIONS

1. În ce privește acuzele orale se poate confirma cu o confidență de 99%, că există o corelație între insuficiența ovariană prematură și acuzele orale. 32,1% dintre pacientele cu menopauză precoce au prezentat acuze orale față de 6% din lotul martor.
2. Pacientele cu insuficiență ovariană precoce au avut un flux salivar nestimulat (bazal) inferior femeilor din lotul martor și un pH salivar mai scăzut.
3. Se poate afirma cu o confidență de 99% (p=0,000) că există o corelație între insuficiența ovariană prematură și suspiciunea de candidoză orală.
4. Confirmarea candidozei orale pe mediul de cultură Sabouraud a fost la 13,2% din pacientele cu insuficiență ovariană precoce și de 2% din lotul martor. Rezultă o corelație pozitivă între prezența candidozei orale și insuficiența ovariană prematură (p=0,024).
5. În menopauza precoce prevalența crescută a candidozei orale s-ar putea datora hipoestrogenismului, scăderii pH-ului și fluxului salivar.
6. Tratatamentul de substituție estrogenic în insuficiența ovariană precoce ar putea preveni și trata manifestările orale la aceste paciente. Pentru acest deziderat sunt necesare studii clinice randomizate, controlate pe termen lung care să dovedească beneficiile tratamentului de substituție estrogenic asupra disconfortului oral în menopauza precoce.

### BIBLIOGRAPHY

1. Mehta S and T. Wang - Intermittent ovarian and thyroid failure and spontaneous twin pregnancy. Ann Clin Biochem, 2008; 45(3): 331 - 334.
2. Gallicchio L S, Miller, T, Greene H, Zacur JA. Flaws - Premature ovarian failure among hairdressers. Hum. Reprod. 2009; 24(10): 2636 - 2641.
3. Christin-Maitres M, Pasquiez B, Donadille P, Budrard R- Insuffisance ovarienne premature. Ann Endocrinol. Orphanet. Dec. 2006.

## CLINICAL ASPECTS

---

4. Leimola-Virtanen R, Pennanen R, Syrjänen K, Syrjänen S - Estrogen response in buccal mucosa - a cytological and immunohistological assay *Maturitas*. 1997, 27, (1), 41-45
5. Välimaa H, Savolainen S, Soukka T, Silvoniemi P, Mäkelä S, Kujari S, Gustafsson J-Å and Laine M- Estrogen receptor- $\alpha$  is the predominant estrogen receptor subtype in human oral epithelium and salivary glands. 2004, *Journal of Endocrinology* , 180, 55–62.
6. Blaylock JM, Jones LE, Lesho E, Cash B, Decker CF. Discomfort with swallowing. *Am J Med*. 2009, 122(8):726-8
7. Goswami D and Gerard S. Conway- Premature ovarian failure, *Human Reproduction Update*. 2005, 11(4):391-410.
8. Bjorling DE, Beckman M, Clayton MK and Wang ZY Modulation of nerve growth factor in peripheral organs by estrogen and progesterone. *Neuroscience* . 2002, 110 155–167.
9. Jukka H. Meurman, L Tarkkila and A Tiitinen. The menopause and oral health *Maturitas*, 2009, 63, (20), 56-62.
10. Agha-Hosseini F I, Mirzaii-Dizgah A, Mansourian M, Khayamzadeh A, - Relationship of stimulated saliva 17 $\beta$ -estradiol and oral dryness feeling in menopause. *Maturitas*, 2008, 62, (2), 197-199.
11. Eliasson L, Carlén A, Laine M and Birkhed D- Minor gland and whole saliva in postmenopausal women using a low potency oestrogen (oestriol). 2003. *Archives of Oral Biology* 48 511–517.
12. Van Der Bijl P. ; Van Eyk A. D. Thompson I O C -Permeation of 17 $\beta$ -estradiol through human vaginal and buccal mucosa Annual meeting of the American Academy of Oral Medicine , 1998, 85, (4), 393-398.
13. Laine M and Pienihäkkinen K - Salivary buffer effect in relation to late pregnancy and postpartum. 2000. *Acta Odontologica Scandinavica* ,58, 8–10.
14. Ghezzi EM, Wagner-Lange LA, Schork MA, Metter EJ, Baum BJ, Streckfus CF & Ship JA 2000 Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy. 2000 . *Biological Sciences and Medical Sciences*, 55, 34–42.
15. Leimola-Virtanen R, Salo T, Toikkanen S, Pulkkinen J and Syrjänen S. 2000 ,Expression of estrogen receptor (ER) in oral mucosa and salivary glands. *Maturitas*, 36 131–137.
16. K. Borhan Mojabi, M. Esfahani , H. Jahani Hashemi - Evaluation of Unstimulated Salivary Flow Rate and Oral Symptoms in Menopausal Women, 2007, *Journal of Dentistry*, Tehran University of Medical Sciences, 4, (3), 105-109.
17. Esfahani M, H. Jahani Hashemi Evaluation of Unstimulated Salivary Flow Rate and Oral Symptoms in Menopausal Women . 2007, *Journal of Dentistry*, Tehran University of Medical Sciences, 4,(3) 110 – 114.
18. Silverman S, Eversole LR, Truelove EL. *Essentials of Oral Medicine*. Canada: BC Decker Inc; 2002. 256- 260.
19. Dodds MW, Johnson DA, Yeh CK. Health benefits of saliva: a review. *J Dent* 2005 Mar;33(3): 223-33.
20. Frutos R, Rodríguez S, Miralles L, Machuca G. Oral manifestation and dental treatment in menopause. 2002, *Medicina Oral*, 7, 26-30.
21. Ghezzi EM, Wagner-Lange LA, Schork MA, Metter EJ, Baum BJ, Streckfus CF - Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy women. 2000 *J Gerontol A Biol Sci Med Sci*, 55(1), 34-42.
22. Sharon V, Sharon NF - Oral candidiasis and angular cheilitis *Dermatologic Therapy* , 2009, 23 (3), 230 – 242
23. López M J F, García Valle S, García Iglesias AA- Periodontal aspects in menopausal women undergoing hormone replacement therapy .2005, *Med. oral patol. oral cir. bucal* (Ed.impr.), 10, 2, Valencia.