Correlations between gonadotropins level, vaginal cytology and menopause vessel-active phenomena

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Abstract
Introduction: Vessel active phenomena from menopause as hot flushes have unknown cause but is demonstrated that the hormone substitution treatment has a very good efficiency in the disproof of the symptomatology. Objectives: To establish if there is a correlation between gonadotropins level, the presence of the vessel active manifestations and the atrophy of the vaginal epithelium in menopause. Material and Methods: The study design is cross-sectional, done on the 40 and 60-year-old women from the general population list of a family doctor. We studied the blood values of LH and FSH and the vagina cytology and the relations of these parameters with the presence of hot flushes and others vessel active phenomena in menopause. Results: The group consists of 136 women aged between 40 and 60-year-old. Their blood tests prove: LH with normal levels in 79% of cases, FSH has high values in 85%, the vagina cytology marked out the epithelium atrophy in 76% of cases. Discussion: The augmentation of the FSH values is associated with the presence of hot flashes. The ratio LH/FSH under 0.40 is strong associated with vessel active phenomena (p-value 0.000012). We could not establish a statistical correlation between the presence of the vessel active phenomena and vagina atrophy (p-value 0.098). Conclusions: Vessel active manifestations on the menopause have morphological substratum. The increase of FSH is statistic correlated to the vessel active disorders. It is possible that FRH be the trigger for the hypothalamic thermo detection.

Keywords: gonadotropin, vessel active phenomena, vaginal cytology, menopause.

Introduction
The menopause is an important period from the women life cause by losing of the reproductive capacity and evidenced by amenorrhea and other specific clinical manifestation. Once with the life hope increasing of the population, the period that the women live in menopause is prolonged, meaning one third or more from the whole women life [1]. From here, arrive the concerning of the doctor regarding the women life quality also in this delicate period.

From the menopause short-term consequences, a vessel active symptom (hot flushes and night sweats) represents the most common reasons for encounter [2]. Together with these, in postmenopause could arrive also urinary and genital symptoms, sleep perturbation, memory disorder, and disposition alteration [3]. The urinary and genital symptoms are due to the epithelium atrophy that favors local infections [4].

The causes of the menopause symptoms remain a research fascinating domains in which, there are for sure many things to tell, representing an equation in which many unknown quantities have to be discovered [5]. The subject, which confronts the most with problems created by vessel active modifications in menopause, is family medicine. The patient with flushes passes through a delicate period of time and confronts with a so called resistance on behalf of the society and sometimes family, especially if the husband is still in a sexual active period. Even though many specialists consider that vessel active manifestations of menopause are psychological determined, the family doctor who knows his patients before their menopause cannot easily accept this kind of thinking. The transformation of the joyful, balanced and full of life woman into a depressive one, with flushes, sweaty, anxious, which does not recognize even herself sometimes, cannot be accused only for the disappearance of the menstruation.

The research motivation: Knowing about the theories, which explain the apparition of the vessel active modifications concerning the woman in menopause [6–9] and their pathogenic certainty, we have came to the conclusion that we should study the pattern of the hormonal level of the gonadotropins at women older than 40 years, who appear on the capitulation list of the family doctor. We would have liked to know if there are any correlation between hormonal levels and vessel active modifications, considering an advantage the fact that the people we have studied were not selected, as it happens in other specialty services (endocrinology, geriatrics, cardiology, etc.). We also wish to decide whether there is or not a correlation between these, the vessel active manifestations and the atrophy of the vaginal epithelium.
Material and Methods

The design of the study is cross-sectional; it will unfold on a 12 months period, between January 1st, 2007 and December 31st, 2007 and will be done considering all people.

We have studied a group of women between 40 and 60-year-old chooses from the capitation list of the authors. The including criteria in the study was the perimenopausal age (five years before and after the theoretical age of menopause installation). We have found a number of 287 persons who belong to this criteria; from these were randomly chosen, by computer, a number of 150 persons from whom samples of LH and FSH blood were taken (the group was limited because of the financial problems). Hormones dosage have been done in “Buna Vestire” Polyclinic Laboratory in Craiova (which sponsored this research), accredited ISO 2007; the normal hormonal values had as a reference the value of the kits used by the laboratory. There have been used the personal data of 136 persons, 14 cases being lost because of the lipemia or hemolised serum (which can modify the results) and also because of the patients refusal to take part in the research. Personal data and symptomatology have been found by a family medicine resident physician, who has been trained concerning the proceeding of questioning the patients about the vessel active phenomenon. The vaginal cytological examination has been realized only on 38 persons (28%). The encoded data were filled out in Excel tables and have been statistically studied with EPI6.

Results

The studied group included 136 persons, women between 40 and 60-year-old, the age average being 47±2.33-year-old. From these, 35 persons (26%) have menstruation, 56 persons (41%) have physiological menopause for more than three years, eight persons (6%) have recent physiological menopause (for maximum one year), and 37 persons (27%) have surgical menopause (Figure 1).

From those women who have surgical menopause, 29 persons (79%) suffered a total hysterectomy with a bilateral anexectomy. The vessel-active symptomatology specific for the menopause has been met in 56% of the studied cases and consisted in flushes, cutaneous rush, headache, dizziness, suffocation sensation and the accompaniment panic.

The luteal hormone dosage (LH) has shown normal values in 79% of the cases (107 persons) and higher values than the normal at 29 persons (21% cases) (Figure 2).

Values have been for 1.08–5.37 bigger than the allowed limit of LH and have been met on 25 women (87% cases) who had menstruation and only four women (13%) on menopause. From those women with high LH values, 44% (13 women) had disorders in the menstrual flux (maybe preclimax disorders) and only 11% (three women) had vessel-active disorders.

The follicle-stimulating hormone dosage (FSH) has shown normal values in 15% cases (20 women) and bigger than normal values in 85% cases (116 women) (Figure 3).

Women who had menstruation, which presents metrorrhagies, sweat and other preclimax disorders have raisings of 1.57–5.37 of LH values and 3.9–6.9 of FSH values (Figure 4).
Vessel-active disorders, especially flushes and sweat that appear in climax are associated in 72% with high values of FSH; women on menopause who do not have vessel-active disorders have 100% normal values of FSH (Figure 5).

In conformity with the normal values offered by the laboratory (producer specification) the ratio LH/FSH in the menstrual period is: in the follicular phase, 0.75–0.80; in the luteal phase, 0.33–0.81; in the ovulatory phase, 0.83–1; in the menopause the ratio is 0.94. In the present study, the ratio LH/FSH has values situated inside the normal limits for 78% from women still having menstruation; 22% have sub unitary values without could associate vessel-active disorders. For the women having menopause, the ratio LH/FSH has higher values in 4% from cases (without vessel-active disorders), normal values in 4% from cases (without vessel-active symptoms) and sub unitary values in 92% from cases (Figure 6).

Among the persons with sub unitary values 80% presented vessel active manifestation and 20% does not have clinic accuses.

The cytology evidenced different aspects do to the FSH and LH level of the secretion. Thus, it was evidenced on the smear two types of cytological aspects:

Smear with pavemental superficial and intermediary cells with low diminish of the number of superficial cells, the majority being immature, basophile, in the favor of intermediary cells (Figure 7). In the same time, the polymorphonuclear leukocytes are low represented. This aspect was seen at the women presented normal values of the ratio LH/FSH (4% of cases).

Smear constitute almost of intermediary pavemental cells, rare superficially one and parabasal (Figure 8). The background of the smear was clean, inflammatory exudation consist of polymorphonuclear leukocytes is quantitative reduced. In the present study, the women with this type of atrophy (atrophy with intermediary cells) was those one who has supra unitary values of the ratio LH/FSH.

The vaginal cytology evidenced the presence of the vaginal mucosa atrophy at 29 persons (76% from the study sub group), the repartition dependent on hormonal status being as follow: 15 persons (52%) has physiological menopause over three years, eight persons (27%) has in present menstruation, three persons (11%) has surgical menopause and two persons (10%) has physiological menopause over one year (Figure 9).
The atrophy aspect was variable. Therefore, the women that still have menstruation, those with physiological menopause under one year and a part of those with physiological menopause over three years (five cases) presents on smear both of superficially pavemen
tal and intermediary cells and parabasal in a variable proportion. The number of the parabasal cells was,
however, bigger on the smears of the persons at menopause over three years than the others; significant
is that there are no basal cells on the smear.

For the rest of the women situated at menopause over three years (and age between 57–60-year-old),
the cellularity of the smear consist on the domination of
the parabasal cells (atrophy with parabasal cells), being
evidenced also frequent pavemenal intermediary cells
and rare superficially cells (Figure 10).

Also, we identify on three cases reactive benign
cellular modifications: hypertrophy of the nuclei CPI of
two or five times (parabasal-like cell); intermediary
cells with small nuclei; cytoplasm auto destruction –
presence of necked nuclei; orange or eosinophil
cytoplasm (Papanicolaou stain); abundant inflammatory
exudation with polymorphous nuclear cells; the content
of the smear is dirty, basophile and granular; material
with aspect basophile, amorphous, type named “blue
bobs” (degenerated BP-cell or condense mucus).

Discussion

Over 40-year-old, we observe that 3/4 of women are
in menopause; this thing, related to the literature data,
having the significance of the tendency to decrease
the menopause installation age [10]. We concern oneself
with a high number of surgical menopause (almost 1/4
from the study women), situated in the age interval of
45–54-year-old; a large number of these one have also
ovariectomy, that may lead to the precocious
increase of gonadotrops hormones’ level.

Hot flushes arrive at more than half of studied
women fact that confirm data from specialty literature
where is mentioned that they occur on 75% of
menopausal women and the mean age is 3.8 years [11].
The frequency, duration and intensity of hot flushes
register important individual variations but, in general,
the duration is for four minutes [12]. In conformity with
literature data, in 30% of cases the symptomatology
decrease in few month, in 60% of cases it will improve
in 4–5 years but on 10% from women, they may
continue for many years [13], even to 40 years from the
moment of the menopause installation [14]. The hot
flushes are experienced by the woman as a hard hot
sensation, especially on the half top of the body:
the head, cervical region and thorax accompany by
swallow, anxiety, palpitations and skin redness.
The menopause vessel-active phenomena could affect
the women working capacity, her social life; sleep
quality and can deepen the negative psychosocial
consequences by coming down the women life quality
[15]. Inside the hot flush, the skin temperature is rising
such as the blood debit. These demonstrate the
peripheral vessel dilatation, which is a physiologic
characteristic element of the menopausal vessel active
phenomena; the modification is seen in different body
regions [16]. It is also registered both of the swallow
augmentation and of skin conductance (electrical
measurement of the swallow gradient) [17]. A recent
acquirement for understanding the complex pathogenic
mechanism of the hot flushes is represented by the
demonstration of central increasing temperature that
precede with few the installation of the peripheral vessel
active symptoms [18].

The pathogenic of the hot flushes is not elucidated
until now, the literature data being inconstant. This
thing stimulates performing the present study. Starting
from the idea that a numerous others studies appreciate
the relation between estrogen and progesterone on a
hand and vessel-active disorders on the other hand, we
arrive on the actual belief that there is no correlation
between these one [19]. One of the theory marks that
the significant decrease of the estrogens in the meno
pause due the vessel active phenomena, fact sustained
by the incontestable benefit of the replacement treat
ment with estrogens. Even so, there is no correlations
statistic significant between plasmatic levels of the
estrogens at the symptomatic menopausal women com
pared with the non-symptomatic one [20]. Furthermore,
pre puberty girls, even they have very low plasmatic
levels of the ovarian estrogens, they do not have vessel
active phenomena [21]. Another theory takes in count
the value of the luteal hormone (LH) that increase
significant also from the pre menopausal period (once
with an ovulatory menstruation installing) [22]. There
are opinions that imply the opioid system in the
pathogenic of the menopause hot flushes, but literature
data are inconstant [23]. The theories that sustain the
vessel active symptomatology based on implication of
the hypothalamic “thermostat” explain the pathogenic
via the thermo genesis compound which increase the
central temperature and, as result, appear reactive
phenomena consist on vessel dilatation and heavy
sweats [23–25]. Very recent studies suggest the possi
bility to be efficient the blockage of the star gland in the
postmenopausal vessel active symptomatology impro
vement [26]. The mechanism is based on interruption of
the conjunction between Central Nervous System and
Sympathetic Vegetative Nervous System, permitting in
this way the resetting of the adjustment mechanisms for

Figure 10 – Atrophy with parabasal cells (telatrophy)
(Papanicolaou stain, 200×).
the body temperature. In the menopause, the pattern of the hormone is due to follicular involution, which induces the decrease of the ovarian androstendione production (progesterone and 17-beta-estradiol) and follicular Inhibine. All of these causes, following the negative feedback effect, increase the pituitary Gonadotropins (LH and FSH) and decrease the hypothalamic releasing factors (GnRH and FRH). Starting from this real fact, we correlated the dosable hormonal values, in the clinic laboratory, with the vessel active manifestations. Discussions regarding this fact refer to three categories of assessments: the ones, which refer to the luteinizing hormone (LH), the follicle-stimulating hormone (FSH) and the ones, which refer to the LH/FSH rapport.

The LH values are generally normal in our research, the raisings appear especially at women who have menstruation and those are not correlated to the presence of the vessel active symptoms: OR=0.13 (0.01–1.14); RR=0.38 (0.12–1.26); p-value=0.023. The large values of LH associated to large values of FSH correlate with the menstrual flux disorders. Therefore, at women with menstruation, where LH values raise with over 1.5 and FSH raise with over 3.9, an ovulatory menstruation, which cause physiological menopause, might appear.

The raise of FSH over normal values of menopause associate with the presence of flushes (p-value = 0.00099); the normal values of FSH are a strong pointer to the absence of vessel active accuse. The intensity of the vessel active phenomenon could not be encoded (we considered the appreciation as being subjective), that is why we could not establish a correlation between the raising level of the number of hormones and the intensity of clinic manifestations.

The sub unitary ratio LH/FSH it is poor associated with the hot flushes presence in menopause but a ratio under 0.40 is strong associate with vessel active manifestations: OR=8 (1.17–63.57); RR=2.17 (1.06–4.44); p-value=0.0097. That means that when a woman at menopause has a normal value of LH the rising twice time of a FSH over the normal value for menopause is a predictive factor for appearance of vessel active phenomena. This sustains that FSH and not LH could be implied in the pathogens of vessel active problems in the menopause. In this way, we can explain the appearance of hot flushes in men in the period of andropause, because the common element for men and women situated on the hormonal decline is the decrease of Inhibin, substance produced by the both gonads in the period of their activity; the role of this one is to inhibit production of FSH. The absence of Inhibin produces the evident rising of FSH and, reactive, influence the concentration of GnRH and more of the hypothalamic FRH.

We consider that the reason for starting the vessel active phenomena is FSH by it’s implication on the axis neurological and hormonal, possible through a complex mechanism which need to be elucidate for the understanding also the others phenomena (the appetite modification, getting weight, behavior modification or vessel-active phenomena especial hypertension) that influence the women life in menopause. Will be recommended a prospective study in the way to follow the relation between the gonadotropins high hormonal levels and vascular events appeared in the menopause.

Norepinephrine, founded in high quantity on the hypothalamus at menopausal women [27], mediates both RH-release and neuronal activity of the supra optical and para-ventricular nuclei (from the anterior wall of the hypothalamus), nuclei responsible with the central mechanism of thermo lyses: vessel-dilatation and swallow. Therefore, we sustain a central mechanism of thermo lyses and we combat a thermo genesis mechanism as is sustained until now; the heat field by women is secondary of brutal vessel dilatation with central origin and that is not due by a high production of heat. Vessel dilatation is systemic and “the wave of hot” could be explain by the quickly transport of the heat (tachycardia and hypertension) from the liver to periphery. We can explain why the hot flushes appear on a “cold field” from “serene”. More than this, the women from the study lot don’t describe “shiver” that precede the hot flushes, in no one of the situation, reason for what we put into discussion the theory that sustain the central heat increasing as cause of hot flushes starting.

Some women do not describe vessel active symptomatology. It is possible that in the period of the active gonad life to form a “pattern” of the axis ovarian–pituitary–hypothalamic characteristic for every person (phenotypical), for sure genetic influenced, that establish a certain hormonal level including after menopause appear.

The atrophy of vagina mucosa and secondary clinical manifestations have been encounter in this study on high number of cases (2/3 from the study women from point of view of the cytology) fact that demonstrate the a decrease of estrogens hormones in absolute value, even that the menstruation is still present. On the last one the cytology was similar with that one from the fertile period, excepting the decrease of the number of the superficial squamous cells; in the specialty literature this is named menopause with the persistence of the estrogenic stimulation and arise especial on the obesity women and sometimes on those who have hypertension or diabetes [27]. The cytological aspect find at the patients with smears constitute especial from intermediary cells is named in the specialty literature as atrophy with intermediary cells (estatrophy) and arise in the condition of the relative deficiency of estrogens [27–29]. This aspect is characteristic of pre-atrophic menopause and evidence a hormonal deficiency, the smear being constituted from a mixture of intermediary cells (in different proportion, from 90 to 10%), parabasal cells and basal cells (these one could represent till to 90% from cells) [27].

At ten women, situated at the physiological menopause over three years, smear was constitute almost from parabasal cells, fact that characterized so called atrophy with parabasal cells or telatrophy [28, 29]. From the moment when telatrophy begin, the vagina epithelium start to be very thin (atrophic) and with high susceptibility on infections. The two types of

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At ten women, situated at the physiological menopause over three years, smear was constitute almost from parabasal cells, fact that characterized so called atrophy with parabasal cells or telatrophy [28, 29]. From the moment when telatrophy begin, the vagina epithelium start to be very thin (atrophic) and with high susceptibility on infections. The two types of
atrophy (estiatrophia and telatrophia) are not stages of the same process. Some women could present from the beginning of the menopause atrophy with parabasal cells whereas the others could have as cytological pattern intermediary cells for long time, being possible to change any time the pattern in those with parabasal cells [29].

A gradual decrease in the production of the hormones estrogens from the ovaries is seen in the peri-menopausal years, ultimately leading to the menopause. Symptoms of vaginal atrophy result from a combination of atrophic changes in estrogen dependent cells that line the vagina lumen [28]. The administration of exogenous estrogens (either systemic or topical) is a common treatment for symptoms related to vaginal atrophy [29–33]. Under the influence of estrogens, maturation of the vaginal epithelium is restored. However, the use of exogenous estrogens has several adverse effects and may therefore be contraindicated [34].

We could not establish a statistical correlation between the presence of the vessel active phenomena and the vaginal atrophy (p-value=0.098), fact that sustain again the possible implication of the hypothalamus in the presence of the vessel active phenomena more than gonadic implication. As the literature also sustain, it is possible that the menstrual pattern prove to be a reliable criterion by which to judge the neither extend of estrogen effect or deficiency nor was there correlation between serial colpo-cytology and endometrial histology [35–39].

\section*{Conclusions}

Vessel active manifestations of the woman in the menopause have a morphological substratum; the present study suggests o possible common etiology for the whole vascular manifestations: neurological and hormonal axis, pituitary–hypothalamic stimulated by the hormonal axis, pituitary–hypothalamic stimulated by the increasing of the releasing hormones (factors) and implicit of the gonadotropin hormones. The existence of a correlation between gonadotropin hormones and vegetative manifestations is important for the medical activity, preventive and curative, of the menopausal woman.

The increase of FSH is statistic correlated with the presence of vessel active phenomena opposite to LH that is not a correlation indicator with vegetative manifestation. It is possible that FRH, feedback influenced by high levels of the FSH, to be the link that stimulates that part of the hypothalamus implicat in the thermoregulation, the mechanism of the hot flushes being probably done by central thermo lyses and not thermo genesis.

The trophicity of the vaginal mucosa is under the major influence of gonadic hormones whereas the vessel active phenomena are under the influence of the hypothalamus dysfunction, complying with the neuronal and hormonal personal pattern.

\section*{References}


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