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Effects of hormonal changes on the quality of voice, vestibular and listening skills: an experimental study on young hearing-impaired women with cochlear implant.

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INTRODUCTION

The progesterone and estrogenic hormones, and their inter-dependent fluctuations in a woman's life have always played a dominant role in their physiological development and in the homeostasis of the female body.

It has only recently been shown that the fluctuation of these two hormones plays a crucial role in neurological and psychological development and influences brain function, cognition, emotional state, sensory processing, appetite and more. The capacity that the reproductive hormones have to influence the psycho-neurological processes leads to different systems in the body interacting. [1]

The extensive interactions between the gonadal hormones and the nervous system are well documented in both adolescents and adults. Such manifestations include, for example, the modulation of neuronal excitability by gonadal steroids, both directly and by affecting the neurotransmitter systems and the intrinsic properties of the cytoplasmic membrane[2], sexual differentiation of the brain by exposure to gonadal hormones [3, 4] , estrogen stimulation of neuronal and dendritic growth in various regions of the brain, such as the hypothalamus[5] and the hippocampus[6].

It is therefore clear that hormones regulate and modulate many physiological processes in the body, including the nervous, cardiac, respiratory and gastrointestinal systems.

Hence, it is not surprising that hormonal regulation can also manifest on the sensory level. [7]

Our study aims to investigate, in women with CI, the possible relationship between different hormonal levels during the menstrual phases (follicular / late luteal phases) and their auditory performances. We focused our attention on the trend of electrodes impedance and auditory perceptual abilities, as well as on vestibular problems.

CHAPTER 1

PHYSIOLOGY OF THE AUDITORY, VESTIBULAR AND PHONATORY SYSTEM IN RELATION TO ESTRO-PROGESTONICS FLUCTUATIONS

1.1 Sex hormones and electrolyte changes

Cyclic hormonal changes can affect a wide variety of biochemical processes. In fact, estrogen has been reported to induce hypercalcemia through the action of the parathyroid gland, [8] instead the drop-in estrogen causes a significant loss of bone calcium.[9]
It has also been observed that an increase in the metabolic basal rate and oxygen consumption during the luteal phase was associated with an increase in the use of carbohydrates [10].
During the post-ovulatory phase, the concentration of progesterone is high and appears to have a natriuretic effect[11].
The increase in progesterone after ovulation is followed by a compensatory increase in the concentration of aldosterone[12].

Puja Dullo et al. [13], report a 12.42% decrease in serum magnesium levels in the follicular phase compared to the menstrual phase and a 19.45% increase in the luteal phase compared to the follicular phase.
Therefore, serum magnesium levels were higher during the luteal phase and lower during the follicular phase.
These results are in agreement with the observations of Pandya et al.[14]

The raised estrogen levels could possibly be acting on the parathyroid gland, due to which serum magnesium levels dropped during the ovulatory phase as reported by Pitkin et al. [15]

Pitkin and co-workers further stated that clinical hyperparathyroidism could deplete the body stores of magnesium.

It has been reported that magnesium ions and oxidative enzymes are needed for carbohydrate utilization which increases significantly during the luteal phase.

Increased serum calcium levels during the ovulatory phase may also contribute to the decreased magnesium levels by exerting an effect on the cell permeability.

It is well known that low magnesium levels result in the constriction of cerebral and abdominal blood vessels.

It is, thus, also possible that the water retention (bloating) that occurring during the luteal phase results, in part, from a slight increase in the constriction of the renal arterial vessels.

It has been demonstrated during studies on cerebral peripheral blood vessels as well as on in vitro umbilical-placental blood vessels, that elevated calcium/magnesium ratios induce spasm. [13,16]

In the study of Lanje et al.[17] as well as in that of Mira et al [18] a significant decrease in sodium in the luteal phase is reported, although it is documented that during the luteal phase of the menstrual cycle the sodium-retaining hormone secretion increases.

Possible causes for this change in sodium concentration include the increased concentrations of the antidiuretic hormone in the luteal phase and the antagonistic effect of progesterone to the typical sodium-retentive influence of aldosterone. **[17]**

Although cyclical changes were observed in these electrolytes during the menstrual cycle, all were found within normal physiological limits.

Serum calcium levels were significantly higher in the follicular phase than in the menstrual and luteal phases and those of magnesium were significantly lower in the follicular phase than in the menstrual and luteal phases.

Blood sodium levels were significantly lower in the luteal phase than in the menstrual and follicular phases while serum potassium was higher in the luteal phase than in the menstrual and follicular phases. [17,18,19-22]

Several evidences [23-25] suggested that the ovarian hormones influenced the metabolism of several electrolytes like calcium, magnesium, sodium and potassium during the different phases of the menstrual cycle.

The coming together of these cyclical, electrolytic changes confirmed the datum that many women undergo variation in the balancing of their liquids and electrolytes in their pre-menstrual days.[19,23-25]

1.2 Auditory system

"The auditory system is a miraculous example of micromechanics, sound engineering and a strictly controlled biological milieu."[26]

Several of its features such as tonotopic organization of frequencies, speed and sensitivity of transduction, sound amplification, ability to locate sources of sound in space, the hair cells' capacity to perceive motions of atomic dimensions and a wide range of frequencies, make it a uniquely sophisticated example of sound engineering .[26]

The auditory system, as every other part of our body, does not have a static function. On the contrary, it is continually controlled by specific demands, and it receives its input through hormones and neurotransmitters.[27]

The excitable quality of the sensorial receptors, the neuronal transmission, the ionic mechanisms and the synaptic plastic quality are all probably modulated by signals which reach the auditory system from the rest of the body and so making the best possible use of the auditory function.[26]

In the last years, estrogenic influences on sensory and cognitive functions has been greatly investigated, leading us to abandon the traditional notion of estrogens as exclusively reproductive hormones and introducing us to the idea of them acting as neurotransmitters or neuromodulators in the brain [1.]
Many of the physiological effects of estrogens across species are mediated through estrogen receptors (ER), which interact with intracellular signaling cascades and regulate the expression of genes

involved in the survival, development, plasticity, and function of neurons.[28]

These receptors are widely distributed in distinct areas of the central nervous system, including the cerebral cortex, preoptic area, amygdala, thalamus, hippocampus, and cerebellum [5-8]

Both ERα and ERβ are expressed in the peripheral and central auditory system of mammals .[9-13]

However, the role of each ER in the auditory system is less well known.

They are nuclear receptors and act mainly as ligand-activated transcription factors.

There are two types of ERs, alpha (ERα) and beta (ERβ), which are products of discrete genes (ESR1 and ESR2 respectively) and interact as complementary opposites, constituting parts of a complex dynamic system in the body.

In human, ESR1 is longer than 140 kb split into 8 exons and localized on the chromosome 6q25.1 and its product (ERα) is a 595 aminoacids protein. ESR2 has been mapped to the 14q chromosome and its product (ERβ) is a 530 amino acids protein. Many promoters of ERα and ERβ have been identified in humans, mice and other species. The existence of various promoters explains the presence of different variants of mRNA and ER isoforms, as well as differential expression of receptors in different tissues and cell types.

Estrogen receptors are protective against gentamicin-induced ototoxicity and hair cell death, but the involvement of each receptor is not known .

Hearing thresholds of ERβ or ERα knockout mice do not differ from wild-type mice, but when challenged with noise trauma, ERβ, but not ERα, protects the auditory system.

Thus, the activity of ER may vary depending on whether basal or challenged states are compared.

It is known that these two receptors interact as complementary opposites, and that could be the reason for the lack of effect of estradiol replacement therapy on the auditory function.

To better understand estrogens' effects on hearing, it is important to characterize how the overall hormonal status affects the expression of each receptor type in auditory tissues, as well as behavior.[28]

Physiological and behavioral experiments on animals lead to variations induced by estrogens in reply to the cerebral auditory system, in otoacoustic emissions and in understanding acoustic meaning.

The acceleration of women’s worsening hearing after menopause adds further weight to the influence the estrogens have on the auditory function [29].

Moreover, it was observed that there are significant changes in hearing thresholds during the menstrual cycle phases: improved hearing thresholds were observed in the late follicular phase (the hearing thresholds at high frequencies were better) [28]

The auditory system seems, then, to be sensitive to changes in female hormones by influencing the latencies of auditory brainstem responses, the amplitudes of distortion product otoacoustic emissions, the pressure of middle ear, the function of eustachian tube, and low frequency hearing thresholds.[29,30]

Moreover, Emami et al. [31] observed that there are significant changes in hearing thresholds during the menstrual cycle phases: improved hearing thresholds were observed in the follicular phase (the hearing thresholds at high frequencies were better). [31]

1.3Vestibular system

The vestibular system, along with the auditory system, is impacted by electrolyte fluctuations that affect the homeostasis of the cochlear fluids of the inner ear.

Also with regard to the vestibular system there are studies in the literature that show a correlation between its functioning and female hormones.

Gould et al.,1990 [32]and Ishii et al., 2009 [33]suggested that peripheral vestibular alterations can take place, in a pre-menstrual phase (luteal phase) because of liquid retention in this menstrual phase which results by an increase in the release of estrogens, progesterone and aldosterone.

The presence of vertigo has been reported in the days before the onset of menstruation in which the levels of estrogen, progesterone and aldosterone inside the ear are higher.

The effect of the increase in hormonal levels results, in fact, in the hydrops of the labyrinth with symptoms similar to those which are found in Ménière's Disease [33,34]

The link between hydro electrolytic variations and functional alterations is immediate when we consider that in the inner ear the membranous labyrinth separates two compartments stuffed with extracellular liquids of very different chemical composition.

The cavities of the membranous labyrinth contain the endolymph, while the spaces between the membranous and bone, the perilymph.

In the mammalian cochlea the endolymph is contained in the middle scale, the perilymph in the vestibular ramp and the tympanic ramp.

Endolymph is a potassium and chlorine-rich liquid (K, 150 to 180 mM) (Cl-, 150 mM), and low in sodium (Na, 1 mM).

Levels of calcium (0.02 mM in the cochlea, 0.20 mM in the vestibule), magnesium (0.01 mM in the cochlea), protein (0.6 g/l in the cochlea) and glucose (<a0.6 mM in the cochlea) are much scarcer in endolymph than in perilymph and plasma.

In contrast, the pH of the endolymph wheres is similar to that of plasma and perilymph.

Another peculiarity of this liquid, the endolymph is hyperosmotic (330 mOsm/l) compared to perilymph and plasma.

This osmolarity is mainly related to the high concentration of KCl.

Perilymph, on the other hand, has a composition similar to an extracellular liquid: the main cation is the Na+(140 mM) and the main anion the Cl- (120 mM), the concentration of proteins is low (2 g/l).

There are differences in composition between the perilymph of the vestibular and tympanic ramp, in fact the concentrations of K+, protein and glucose (4 mM) are higher in the vestibular perilymph than in the tympanic perilymph. With regard to the passive transport of water into the cochlea, different types of aquaporins (for immunohistochemistry) were highlighted in the different structures of the inner ear. These are small integral membrane proteins that allow the selective passage of water molecules in the direction of osmotic flow. The most represented at the inner ear level are the AQP-1 and the AQP-4.

Therefore, different types of electrolytes are physiologically involved in cochlea homeostasis to ensure a balanced ion cochlear environment. It is therefore not surprising that hormonal changes, which affect electrolyte balance, may be responsible for the signs and symptoms reported by patients in the luteal phase.[12]

Experimental studies [35]have suggested that the aldosterone, which increased in the luteal phase, could increase the endolymphatic absorption inside the ear and, in particular, in the endolymphatic sac. The Na+/K+ATPasi pump, the Na+Cl- co-transporter and the epithelial Na+ canals seem to be controlled by the aldosterone and are expressed also in the endolymphatic sac. [36] Besides, the endolymphatic sac increased the Na+ permeability and the Na+/K+ATPasi activity, which potentially contributed to absorbing the endolymph. The numerous variations in internal ear homeostasis may then affect the auditory/vestibular system.

Normal Na^+ flux in the cochlea is only about 1% of normal K^+ flux (Konishi et al., 1978), indicative of the need for less active transport machinery for Na^+ absorption than for K^+ secretion.

This is consistent with the observation of dense vascularization of the stria vascularis (seat of K^+ secretion) compared with the avascular

Reissner's membrane and single-vessel metabolic supply of the outer sulcus. This apparently 'low' transport rate of Na^+ actually reflects the unusually high transport of K^+ transport and does not imply that Na^+ movements are physiologically unimportant.

It is also reported that iron metabolism is also involved in the homeostasis of endolymphatic space involving the volume and acidification of endolymph, and its role has recently been compared to that of K+.

Magnesium is implicated in the permeability of sensory cell membranes, including hair cells, and its deficiency causes a reduction in the electrochemical gradient required for sensory transduction.[37-40]

1.4 Phonatory System

The production of voice is a complex function which depends on multiple systems including a properly functioning neurological system, the respiratory system and an anatomically sound and physiologically active upper airway tract. [41,42]

The larynx is a dynamic structure which can alter its shape and lumen thanks to a system of articulated cartilages controlled by the 10th cranial nerve. Essentially, voice is produced by the vibration of a closed glottis during expiration. The air blast produced by the lungs induce a vibration in the glottis which produces voice which in turn gets articulated in the lubricated supra-laryngeal airway to form speech. This complex mechanism is important to understand as any change in any of these systems brought about by endocrine disorders would have an impact on the physiology of voice production.

The characteristics of speech include voice (audible sound waves), pitch (rate of vibration of the vocal folds), resonance (quality and depth in voice), intonation (variation of pitch without distinguishing of words), tone (pitch variation with distinguishing of words), intensity (pressure of sound), timbre (characteristic tone or quality), and articulation (production of vowels and consonant sounds). [43]

The fundamental frequency (F0) corresponds to the number of vocal fold vibration cycles per second (Hz) and perceived as the pitch of the voice.

The vocal cords in females are short and thin, leading to fast vibration, giving a higher pitch to their voice.

There are changes in the F0 with age with the first change happening at puberty in males.

Thereafter, with advancing age the pitch gets reduced in females and increases in males. The short vocal tract in the females gives to the voice a higher resonance than male voice. [42-44]

Voice is considered as an important secondary sexual characteristic which gives an independent imprint to the character and personality of an individual.

The profound influence of sex hormones on the characteristics of voice is mediated by the hormonal receptors present within the vocal folds and apparatus.[45]

Laryngeal structures are exposed to the external environment constantly leading to alteration in the voice.

There are certain sexual differences about the voice change observed during puberty. Increased testosterone and dihydrotestosterone in males lead to increased bulk of laryngeal muscles and ligaments. This leads to drop in the higher octaves in the pitch of voice and frequent cracking.

In the elderly males, the level of estrogens has a major influence on the voice rather than the prevailing androgens.

A study done in an elderly population, compared the voice characteristics in patients with and without hypogonadism. In patients with low estrogen levels, there is an increase in the mean fundamental frequency and a shift of the frequency ranges with alterations in the highest and lowest frequencies. [46]

In the females, the elevated estrogens and progestogens have minimal effect on the voice during puberty.

The importance of hormonal influence on the female voice is appreciated during the cyclical changes of the menstrual cycle. The voice changes associated with the premenstrual syndrome are grouped under dystrophia premenstrualis[47]

The classical manifestation is the difficulty in singing high notes during the premenstrual period.

There is laryngeal edema due to the high estrogenic state before the ovulation.

However, the relative excess of androgens after menopause may lead to a slight drop in the pitch of the voice.

Other voice changes observed after menopause include huskiness, vocal fatigue and inability to reach high harmonics. These changes are appreciated more in professional singers and teachers who use the voice for living.

Hormone replacement therapy has shown to reverse most of the observed voice changes in postmenopausal females. [48]

It is recognized that the larynx is the target organ of endocrine interactions by all internal secretion glands (hypophysis, pancreas, thyroid, parathyroid, testicle, ovary).

More specifically the target tissue is the subepithelial connective of the vocal cords, where the richness of vessels allows significant circulatory reactions and the presence of large structural spaces facilitates buildup of oozed and exuded. In fact, the typical aspect of endocrine dysfunction is the alteration of the vocal cords that presents itself as generalized edema.

In women, the most frequent endocrine dysfunction is related to ovarian function. The pre-menstrual imbibition of the vocal cords is often the result of the decline of estrogen and progesteron levels that promotes capillary permeability and hydrophilia of connective mucopolisaccarids.

Fatigueal vocal activity, in these periods and in predisposed subjects, can promote the onset of relapsing edemas.

Cytological examinations performed on larynx and vaginal epithelium smears show overlapping variations during menstrual cycle and menopause.

Receptors for estrogen, progesterone and androgens have been found in the cytoplasm and nucleus of the glands and in fibroblasts.

Larynx has been shown to be a target organ for other hormones, as well as sexual ones.

For example, thyroid hormone receptors, clinically associated with speech variations, were found in the human larynx.

Steroid hormone receptors are in fact part of a superfamily that also includes receptors for thyroid hormones, vitamin D3 and retinoic acid. For this reason, some hormones can bind to more than one receptor belonging to the same superfamily. Biological efficacy will depend on the affinity for receptor and the concentration of the steroid.

Finally, progestogens compete with androgens both at the receptor level and for the use of alpha-5-reduttasis, thus acting simultaneously as antiandrogens and antiestrogens.

Female life is intimately related to hormonal variations.

Dynamic variations of the three sex hormones occur during the different stages of life: they begin at puberty, fluctuate during reproductive age and decline drastically into menopause.

Such hormonal changes affect the larynx and vocal cords which in turn affect vocal production.[49]

Many studies have investigated the effects of the menstrual cycle on the voice by describing changes before menstruation or in the ovulation period.

Variations in vocal fatigue include decreased dynamic range with loss of vocal force, and higher-spectrum harmonics. These variations have been reported mainly by vocal artists, while among those who use the voice in a non-professional way, such disorders appear less frequent. In a 2002 study, Chernobelsky[50] compared 15 female singers with vocal abuse disorders to 15 singing students with proper vocal output. Both groups reported mild voice problems before the start of the menstrual cycle. The authors reported a mild edematous and erythematous state of the vocal cords, as well as a cords hyposthenia demonstrated with laryngeal stroboscopy and EGG.

Vocal symptoms and instrumental correlates were prevalent in the voice-abusing group, suggesting that vocal abuse behaviors aggravate slight premenstrual vocal variations, thus increasing the risk of vocal, even organic, pathologies.

Women who exhibit symptoms of premenstrual syndrome appear to have a greater variation in the fundamental frequency (F0) at this stage.

In addition, women have a higher incidence of speech disorders because pregnancy, premenstrual syndrome, use of oral contraceptives, peri/postmenopausal period and certain medications (antipertensive, anticonvulsants, antidepressants, antihistamines and anti-acids) can cause lowering of the voice.[48,52,53]

In a recent study, LI X. et Al.[54], analyzed voice changes in 29 women with low pitch during pregnancy. Clinical features, voice characteristics and laryngoscopic signs, changes in hormone levels in 29 women with low pitch during pregnancy were retrospectively analyzed and compared with data from 30 age-matched nonpregnant controls.

Compared with controls, there was a statistically significant reduction in pitch in the patients. This occurred in the first trimester of their pregnancies in 7/29 patients (27.5%), in the second trimester in 17 (58.6%), and in the third trimester in 5 (17.2%). Of 22 patients who had data on hormonal levels, 9 patients (40.9%) had abnormal hormone levels. Of the remaining seven patients with no hormonal data, 3 had acne, rough skin, or thick hair during pregnancy. Among the 23 patients who were followed up, 1 (4.3%) recovered to normal pitch 6 months postpartum, 12 (52.2%) had higher pitch but this did not return to normal levels, and 10 (43.5%) showed no significant improvement in phonation.

In conclusion the authors reported low pitch during pregnancy occurs most frequently in the second trimester and is more likely to occur when the fetus is a boy. Mucosal edema of vocal folds is common and is closely related to changes in hormone levels during pregnancy. After delivery, the pitch of some patients can improve, and some return to normal pitch.[54]

Therefore, fluctuations in hormonal levels have a great impact on the voice so much as to alter histology and laryngeal function.[55]

According to a study by Abitbol et al.[56], 33% of women experience Premenstrual Vocal Syndrome characterized by vocal fatigue, reduction of vocal range, hoarseness (most evident in voice professionals[57,58]), loss of higher frequencies, vocal dysfunction, dry throat, raclage, lowering of the vibration frequency of the vocal cords. These symptoms are associated with vocal cords congestion, microvarices, edema of the vocal cords and loss of cord vibration amplitude. In the premenstrual phase there is also an increase in the frequency perturbation index compared to the follicular phase, the polysaccharides, in the vocal cords, break and bind the water more easily, favoring the accumulation of fluids.[57,59]

Rajet et al.[60] studied in particular the changes in the vocal parameters corresponding to the different hormone levels during childbearing age and menopause

They found that the best vocal quality is in the third stage of the menstrual cycle (ovulatory phase ranging from the 13th to the 15th day) where higher estrogen levels result in a higher vocal range and a higher sound/noise ratio; instead the "worst" item would be in the fifth phase (premenstrual phase that goes from the 24th to the 28th day), characterized by the lowest estrogenic levels.

CHAPTER 2

MATERIALS AND METHODS

The study was carried out by analyzing a group of women, at fertile age, recruited at the Unit of Audiology (University of Federico II, Naples).

Only women with profound bilateral hearing loss and rehabilitated with mono-lateral CI from at least 5 years and a history of regular menstrual cycles were selected.

Regular was defined as being foreseeable within three days and a normal cycle length (defined as 26-30 days) from at least a year before the study.

Women were analyzed during both the follicular and luteal phases which represent menstrual phases with very different hormone levels: in the follicular phase the estrogen and progesterone are in the lowest level, while in the late luteal phase the progesterone is at its maximum level.

We then selected eight female patients, aged between 18 and 45. None of the selected females smoked and had not taken, in the last six months, oral hormonal contraceptives.

Seven of these had had their cochlear implant on their right side with only one of them having had it on the left side. The participants were evaluated between their 5th and 7th days (the follicular phase) and between the 24th and 27th days (late luteal phase) of their menstrual cycle. All of them reported, in anamnesis, particular symptoms in the days preceding the beginning of their menstrual cycle (late luteal phase).

Specifically all eight women referred to a feeling of a lessening in their auditory ability, with four of them lamenting instability and a feeling of a thick head, two others referred to feelings of vertigo linked to neuro-vegetative symptomatology while the remaining two had an increase in pre-menstrual headaches.

None of the eight patients lamented these symptoms in the follicular phase.

Follicular and luteal phases were confirmed by performing hormonal dosages of progesterone and estradiol.

All the women in the study were followed for a year before starting the research, indicating they all had a normal ovulatory cycle.

An audiological, vestibular and phoniatric evaluation was performed, according to standard protocols, on all eight selected patients.

2.1Audiological evaluation:

- Pure tone audiometry at the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 6000 Hz.
- Speech audiometry using single bi-syllabic words in common use, taken from an open list of words which were also phonetically balanced.

2.2 Vestibular examination:

Vestibular examination was realized by videonistagmoscopy.

We evaluated: spontaneous-positional nystagmus with and without fixation, Vestibule-Ocular Reflex (VOR) to slow rotation, Head shaking Test and Vibratory Test, with three stimulation trials of each mastoid, using 100 Hz with each stimulus lasting about 5–10 s.

2.3 Evaluation of electrodes impedances

To measure the impedances of the electrodes, a digital cochlear implant directly linked to the sound processor was used.

The measuring process was controlled by a computer and the interfaces were supplied by each cochlear implant companies.

The measuring process was carried out by the software of the implant and, in the specific case the 3.0 Soundwave was used for the Advanced Bionics company implants, and 4.1 Custom Sound for the Cochlear company implants.

All audiological tests were repeated in the follicular and luteal phases for every patient.

2.4 Phoniatric evaluation

- Laryngo-videostroboscopy, with rigid optical fibers 70° angle
- Evaluation of the disability grade through the administration of the GIRBAS scale, for the perceptive assessment of the voice (Fig.2)
- spectroacoustic analysis of the voice with PRAAT method.

Patients were asked to produce a sustained /a/ for at least 4 sec, in a normal conversation voice level, with constant intensity and frequency. The recording of the sound signal took place via a dynamic, unidirectional microphone at a fixed distance of 10 cm from the lips. The analysis of the voice emission was carried out using the PRAAT program on Windows 9x (NT) Model 2000 method (P. Boersma et D. Weenink).

The data were collected following the same parameters in the follicular and luteal phases.

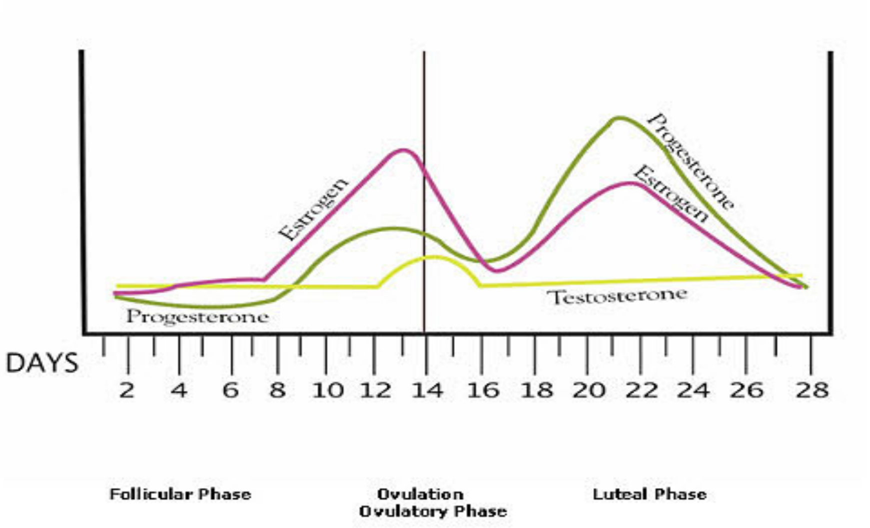


Fig.1

GIRBAS SCALE	**0** **no alteration**	**1** **mild alteration**	**2** **moderate Alteration**	**3** **severe alteration**
G: GLOBAL DEGREE OF DISPHONIA				
I: DEGREE OF VOCAL INSTABILITY				
R: ROUGHNESS				
B: BREATHUNESS				
A: DEGREE OF VOICE ASTHENIA				
S: STRAIN (PRESSED VOICE)				

Fig.2 The GIRBAS scale evaluates five qualitative parameters: general degree of disphonia, voice instability, hoarseness, breathiness (turbulence noise of air escaping through the incompletely closed glottis), vocal asthenia, pressed voice.

For each parameter, a score is provided on a scale between 0 and 3, where 0 represents the eufonic condition, while 1, 2, and 3 correspond to mild, moderate, and severe deviance degrees, respectively.

CAPITOLO 3

RESULTS AND DISCUSSION

3.1 Hearing performance and the measurement of electrical impedance

All the examined patients lamented a lessening in their auditory ability, in the luteal phase, and they asked to carry out a fitting session for the cochlear implant.
Protocol imposed no adjustment of the setting until all the necessary data from the study had been gathered together.

Performances in the audiometric examination were substantially superimposable in both the luteal and the follicular phases. In the follicular phase an average reply of 4.3 dB was noted which was bettered only in the 1000 HZ, with regard to the luteal phase.

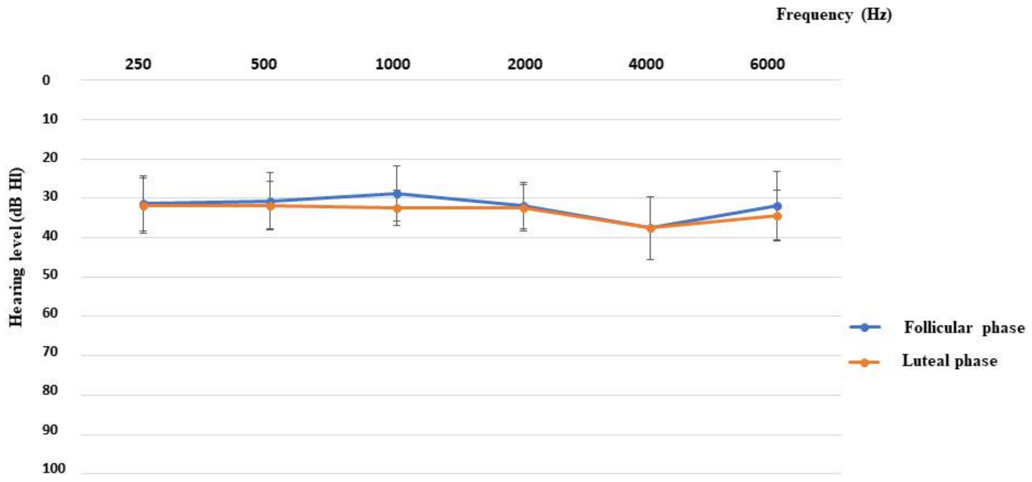


Figure 3. Average of the tonal audiometric examinations in 8 patients in the follicular phase and in the luteal phase.

In the Figure 3 are shown the performances in the pure tone audiometry: for all patients they were similar in both the luteal and the follicular phases.

The trend of the performances in the audiometric vocal examination were instead systematically worse for all the patients in the luteal phase (Fig.4-5-6)

In Figures 4 and 5 are reported the speech audiometry results showing the qualitative response with a cochlear implant in the two phases of the menstrual cycle, respectively in the follicular and luteal phase. In particular, in the follicular phase (Figure 4) it can be observed that 4/8 patients (50%) (AB,DG,TF,PL,) have a speech recognition threshold of 100% at the intensity of 50 dB ; 1/8 patients (TC) 90% at 70 dB;1/8 (DV) 70% at 50 dB; 1/8 patients (CR,) have 50% at 70 dB, 1/8 (RF) 0% at 60 dB.

in the luteal phase (figure 5) it can be observed that only 1/8 patients (AB)have a speech recognition threshold of 100% at the intensity of 50 dB; 1/8 patients(DG) 100% at 60 dB; 1/8 patients (TF) 90% at 50 dB; (PL) 1/8 patients 90% at 50 dB; (DV) 1/8 patients 70% at 60 dB;(TC) 80% at 70 dB; (CR) 30% at 60 dB (RF) 0% at 60 dB.

On average, therefore, it was observed a lessening, in the luteal phase, in their auditory perceptive abilities, with a capacity perceptive reduced by 10% to the various intensities examined. In fact, they asked for the chance to carry out a fitting session for the cochlear implant during the luteal phase.

In Figure 6 it is reported the comparison between the means of the functional response with IC above described.

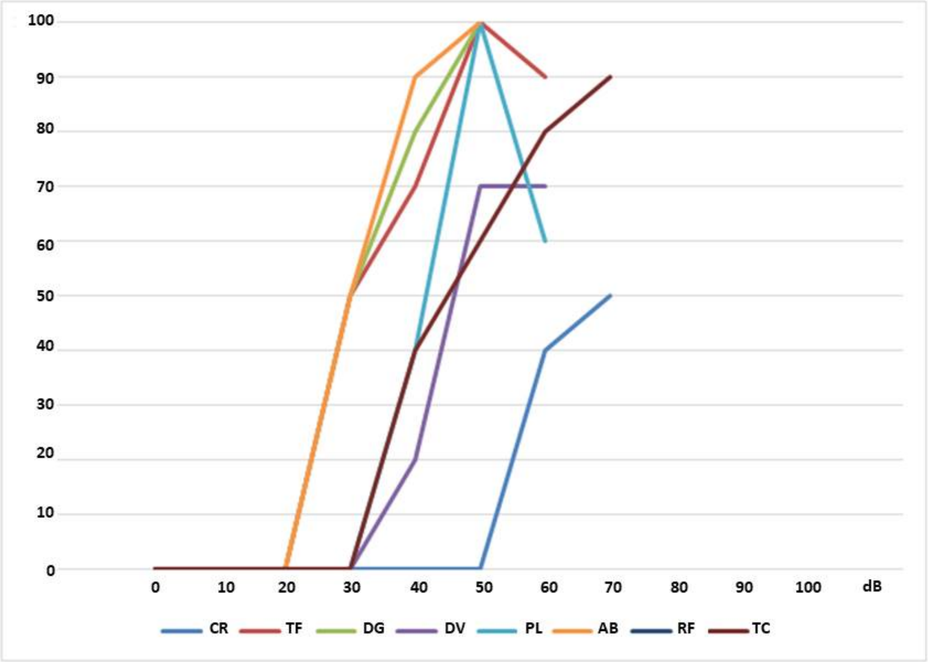


Figure 4. Vocal audiometric examination in the follicular phase.

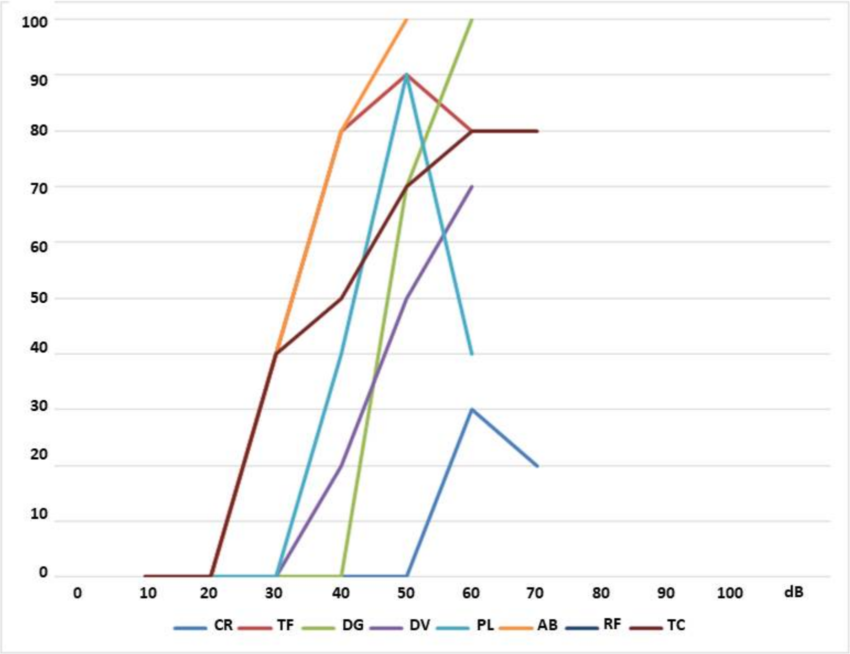


Figure 5. Vocal audiometric examination in the luteal phase.

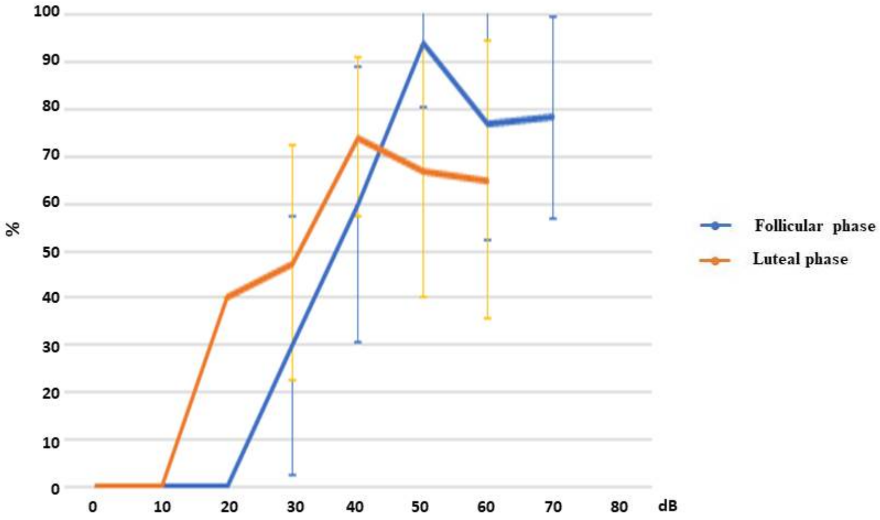


Figure 6. Average of the performances in the vocal audiometry, in the follicular and luteal phases.

Evaluation of electrodes impedances

So as to measure the impedances of the electrodes, a digital cochlear implant directly linked to the sound processor was used.

The measuring process was controlled by a computer and the interfaces were supplied by each cochlear implant companies.

We calculated the average impedance of the electrodes in the luteal and follicular phases (Fig.7).

The results showed a general increase in the impedances of the electrodes in the luteal phase: values reached a maximum increase of 2.55 KOhm.

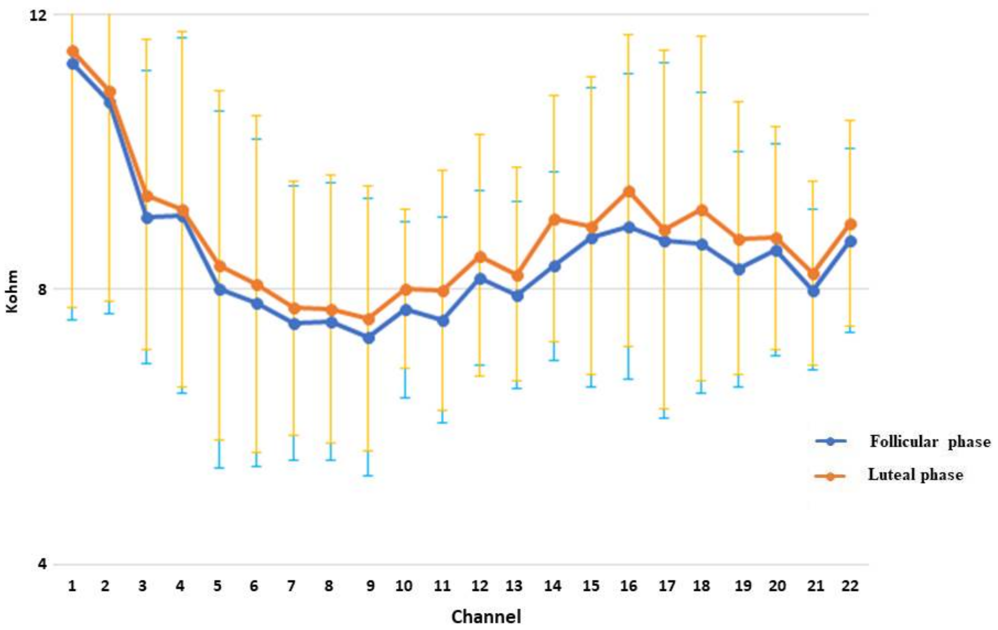


Figure 7. Average of the impedance of the electrodes in the follicular and luteal phases.

Electrical impedance is a physical magnitude that represents the force of opposition of a circuit to the passage of an alternating electric current. The unit of measurement is the Ohm and is measured using the following formula:

$$\frac{V}{I} = Z$$

Where V indicates the voltage, I the current intensity and Z the impedance.

In a cochlear implant, regardless of the transduction strategy and model, electrical stimulation consists of biphasic pulses.

This type of stimulation was chosen to avoid the electrolysis effect. The impedance test, for a cochlear implant, is a routine test that allows to determine the operation of the electrode, that is, whether the electrode is able to produce the stimulus. In this case, the impedance represents the resistance to the current passage generated by the cochlear wall in contact with the electrode.

Continuous stimulation by the electrodes tends to form an end fibrosis, due to the Joule effect. This fibrosis coats the electrodes and still them to the cochlear wall, favoring the passage of the stimulus. Once the right current of stimulation is determined, the impedance should remain constant but there are external phenomena that can result in a variation of this magnitude.

In fact, the lack of electrical stimulation due to non-use of the processor or the closure of a stimulation channel, reduces the fibrosis generated by the Joule effect and thus increases the value of the impedance. Another cause that can generate a variation of this magnitude may be the variation in the ion concentration of the perilymph. The composition of the perilymph mirrors the composition of plasma, and the literature indicates that the concentration of plasma potassium increases at the luteal stage.[18,61,62]

Therefore, about electric impedances, our data showed, in the luteal phase, a homogeneous increase in the impedances of the electrodes over the entire sample which was studied (Figure 7). As has already been said, it is in this phase that the greatest hydro-electrolyte changes can be verified, among which is probably an endolymphatic hydrops.

The hydro-electrolyte environment in which the electrodes were immersed was thus modified, in this phase, altering in part the electric transmission and thus probably auditory performances.

It can be supposed that an increase in the K+ ions in the perilymph, which are normally scarcely represented, may perform a detergent function on the electrodes and may lead to a detachment of the subtle fibrotic area that keeps the electrodes in a stable position and thus an increase in impedances which negatively affects the hearing ability. [63]

With regard to this there can also be included an increase in the water through the aquaporin action which can determine the dilution of the endolymphatic liquids and this can lead to a reduction in its conduction capacity; it has been demonstrated in fact the influence of aquaporin in hydrops . [64,65]

In the luteal phase, as mentioned above, major hydroelectric changes can occur, including endolymphatic hydrops.

Actually, very little information is reported on correlation between hormone alterations and cochlear implant performances, but in one paper it has been reported that aldosterone can reduce impedance changes of CI electrodes.[66]
This is interesting because it is known that, normally, the electrode impedances should not undergo major changes during the life, in fact, it is reported that a reduction in the average electrodes impedances was observed only during the first weeks after implantation and although impedances tended to increase slightly with the use of the cochlear implant, no statistically significant differences were found between the following months.[67]
During the luteal phase, the hydroelectric environment, in which the electrodes are immersed, changes and as a result the electrical transmission is modified, all of which affects auditory performance.

In fact, as already shown in graphs 4 and 5, the performance resulting from the speech audiometry were worse in the luteal phase; on the contrary, the thresholds obtained from tonal audiometry were similar in the two phases of the menstrual cycle.

Failure to alter hearing thresholds at pure tone audiometry(Figure 3), despite the variation in electrode impedance (Figure 7) ,could be explained by the fact that electrical stimulation is within the micro-ampere range compared to nano-ampere in ion current, and would therefore not be relevant to hearing thresholds, but would instead affect the loudness growth and therefore the verbal perception.

The increase in electrode impedance probably contributes but does not fully explain this deterioration.

Recent findings on the link between hormones and the central nervous system can help us clarify these findings.

Hederstierna (2009)[68], in fact, characterized the effects of estrogen deficiency on hearing in women with Turner syndrome, who have a chronic lack of this hormone, crucial trophic support for many cell types including neurons.

The research team detailed the peripheral aspects of hearing loss of patients with Turner syndrome, such as reduced cochlea sensitivity measured with otoacustic emissions, hearing potential (ABRs) and speech recognition scores.

A central role was played by sound localisation tests, where critical processing takes place in the central auditory system, implying problems in central auditory processing as a result of estrogen deficiency in Turner's s.

Price [69] in a 2009 study examined a group of middle-aged female mice and gave them a combined hormone replacement therapy (estrogen, progesterone), estrogen in monotherapy, or a placebo. It was noted that hearing thresholds had decreased for the group taking combined hormone therapy compared to the control groups and compared to the group treated with only estrogen. In many aspects, these results are similar to the results of human clinical trials on women taking combined hormone therapy.

Miranda and Liu[70], studying mouse patterns in postpartum, reveal associations between hormonal changes, auditory processing and vowels of mouse babies. In particular, these authors show that fluctuations in female hormones can drive sound processing of the auditory cortex through dopaminergic and cholinergic neuronal circuit modulations in the cerebral cortex. These changes improve mothers' auditory processing so that they can better feel, feed and treat their progeny.

Indeed the alterations of the cerebral substance during the menstrual cycle certainly play a role. As we mentioned previously, it is confirmed the increase in bilateral gray hippocampal volumes and the increase of the gray matter volumes of the right base ganglia after ovulation (Charitidi et al., 2012).[28]

Moreover, a very recent study on 55 women has shown alterations of the brain substance during the menstrual cycle. In particular, it shows a significant estradiol- dependent pre-ovulatory increase in gray matter volumes of the bilateral hippocampus, but also a significant, progesterone-dependent increase in gray matter volumes of the right basal ganglia after ovulation (Pletzer et al. 2018)[71].

The authors have shown that hormone driven menstrual cycle changes in human brain structure are small, but may be the underlying cause of menstrual cycle dependent changes in cognition and emotion.

In conclusion, therefore, about our results, it is plausible that the lessening in perceptive auditory abilities could be linked to the altered central auditory elaboration caused by an estrogenic fall and moreover to the increase in the electric impedances of the CI.

3.2 Vestibular system

Given the probable influence of ovaric hormones in the different phases of the menstrual cycle on the vestibular function, we searched for vestibular signs that could confirm such effects.
To verify if the menstrual phases can have influence on vestibular working we performed vestibular examination, in the eight women selected, both during the follicular and luteal phases (Table 1).
In the luteal phase, of the 8 patients examined, 4 lamented a feeling of instability and suffering from a "empty head", 2 patients referred to vertigo episodes linked to neuro-vegetative syntomathology, 2 speaking of a feeling of a "empty head" and suffering from headaches.
None of the 8 patients referred to similar symptoms in the follicular phase.
As shown in the Table 1, during the luteal phase all patients showed signs of peripheral labyrinthine suffering, while in the follicular phase the signs of labyrinthine suffering are not present in all patients and when present are less severe.

The numerous variations in internal ear homeostasis may affect the vestibular system and this was probably an expression of the endolymphatic hydrops caused by electrolytic fluctuations because of a retention of sodium.

The collected data, in fact, have shown signs of a peripheral labyrinthine suffering in all the patients. As the literature [33,72,73,74] confirmed, it is a probable expression of the endolymphatic hydrops caused by the electrolyte fluctuation.

More specifically, in the luteal phase, all patients showed signs ranging from the appearance of spontaneous nystagmus, increased frequency of nystagmus already present in the follicular phase, canal-macular malfunction, asymmetry in labyrinthine activity. Table 1.

Patient	**Vestibular Examination in the Follicular Phase**	**Vibratory Test in the Follicular Phase**	**Vestibular Examination in the Luteal Phase**	**Vibratory Test in the Luteal Phase**
R.F.	Geotropic nystagmus on the left, persistent, stationary, partially inhibited. Head Shaking Test : left nystagmus	Re-enforces the left nystagmus	Bipositional, bidirectional side,persistent, stationary geotropic nystagmus, inhibited. Head Shaking Test : left nystagmus	Re-enforces the left nystagmus
C.R.	Omnipositional, persistent, inhibited down-beating nystagmus. Head Shaking Test : negative	Re-enforces the the down nystagmus	Persistent, stationary,inhibited nystagmus to the left. Head Shaking Test : left nystagmus	Re-enforces the left nystagmus
T.F.	Absence of spontaneous nystagmus. Head Shaking Test : left nystagmus	Negative	Up-right, omnipositional, persistent, inhibited nystagmus. Head Shaking Test : left nystagmus	Re-enforces the the right nystagmus
D.G.	Negative	Negative	Bi-positional,bi-directional, persistent, stationary, inhibited nystagmus. Head Shaking Test : negative	Negative
T.C.	Up-beating nystagmus, omnipositional, uninhibited. Head Shaking Test: negative	Negative	Up-beating nystagmus, omnipositional, uninhibited. Head Shaking Test : negative	Re-enforces the up-beating nystagmus
D.V.	Negative	Evokes a right nystagmus	Down-left, persistent, omnipositional, inhibited nystagmus. Head Shaking Test : right nystagmus	Evokes a right nystagmus
P.L.	Up-beating nystagmus in supine and side (left and right). Head Shaking Test : negative	Negative	Up-beating nystagmus with rotational clockwise, omnipositional, persistent, inhibited nystagmus. Head Shaking Test : negative	Evokes an up-beating nystagmus
A.B.	Left nystagmus in supine and left side, persistent, stationary, uninhibited Head Shaking Test : left nystagmus	Negative	Down-beating, omnipositional, inhibited, stationary nystagmus. Head Shaking Test : left nystagmus	Re-enforces the left nystagmus

Table 1. Synoptic table of the signs reported in the Vestibular Tests

Andrews et al.[74] offer multiple explanations:

- aldosterone increases during the premenstrual period and since aldosterone, as well as estrogen, causes water retention, the combined effect of these two substances causes water molecules to move into sensitive compartments of the inner ear;
- seric triglycerides may slightly increase, glucose and fasting insulin levels decrease;
- during late luteal phase, the viscosity of the blood can impair the blood flow of the inner ear and cause changes in the balance of the fluid;
- Increasing the amount of cerebrospinal fluid during the pre-menstrual period could cause an increase in endocranial pressure. This change can affect the inner ear through the cochlear aqueduct, which connects the inner ear to the cerebro-spinal liquor.

As Literature suggests, therefore, endolymphatic hydrops play an important role, it represents a pathologic anatomic finding in which the structures bounding the endolymphatic space are distended by an enlargement of endolymphatic volume.[75,76]

In the cochlea, endolymphatic hydrops is typically seen as a distension of the Reissner membrane into scala vestibuli.[77,78]

Other membranous structures in the ear may also be displaced to varying degrees, including those bounding the saccule, utricle, and ampullae of the semicircular canals.[79] The degree of distension appears to be related to the mechanical compliance of membranous components of the inner ear,[80] with high compliance (mechanically weaker membranes) in the saccule and lower compliance (mechanically stronger membranes) in the semicircular canals. Variations in mechanical compliance of the boundary membranes (analogous to ‘‘weak spots’’ on a balloon) may also explain the considerable variations in degree of hydrops in different regions of the same specimen.[81]

Displacements of the basilar membrane in the apical segments of the cochlea have also been reported, in some patients to a degree whereby the basilar membrane contacts the bony wall of the scala tympani.[82]

Sex hormones essentially play a key role in predisposing to vestibular disorders, it is well known that there are large differences in the incidence of some vestibular disorders between males and females, with females overrepresented in most cases. Two examples where this has become evident recently are vestibular migraine[83] and mal de debarquement syndrome.[84]

However, there is also epidemiological evidence to support a higher prevalence of women for benign paroxysmal positional vertigo, Meniere’s disease (MD), and vestibular neuritis[85,86]

The implications of any differences between males and females in the incidence of vestibular disorders are obvious.

An overrepresentation of females suggests that they are in some way more prone to vestibular dysfunction as a result of specific mechanisms that exist in the female brain and/or peripheral vestibular system.
Therefore, it possible that the optimal treatment for some of these disorders in women requires different methods than those used for men. This might involve taking account of the phase of the menstrual cycle in which the woman presents, using additional drugs in cases where drug treatment is required, or altering drug doses during the menstrual cycle. [87]

Giacomini et al.[88] believe that in patients taking oral contraceptives, the direct cause of suffering from mild paroxysmal vertigo is a disturbed electrolyte balance, changes in endolymph pH, and disturbed metabolism of glucose and lipids resulting from the use of hormonal contraceptives, confirmed by the authors' own studies. According to Mitre et al.[89] the use of hormonal contraceptives may contribute to the occurrence of tinnitus or disorders of the vestibular system. [90]

Some women with Meniere's disease demonstrate exacerbation of symptoms during the premenstrual period.

It is believed that the hormonal stress of the premenstrual period acts on inner ear with Meniere's disease to result in dysfunction.

The hormonal effects of the premenstrual period include alterations in sodium and water balance through changes in plasma estrogen, progesterone, aldosterone, and antidiuretic hormone. These hormonal effects are likely to influence the aquaporin system. Other physiologic alterations of the premenstrual period that can affect the inner ear include changes in thyroid hormone levels and blood viscosity. Migraine, Meniere's disease, and the premenstrual period may be a complex interaction leading to exacerbation of symptoms. [91]

In addition to the possible consequences of an increase in inner ear fluids, it is important to note that estrogen and progesterone levels in the premenstrual phase may affect central nervous system functioning, indirectly altering the optokinetic function. This may occur especially in those areas related to the visual-vestibular interaction, such as GABAA (gamma-aminobutyric acid a) receptors, which is an inhibitory neurotransmitter that binds to specific receptors. Progesterone metabolism may modulate these receptors, altering the transmission in the vestibular nuclei that are involved with the optokinetic, vestibuloocular and vestibulospinal reflexes.[33,92]

Our data, in accordance with the literature, suggest and confirm a role of sex hormones on the complex vestibular mechanism.

3.3 Phonatory system

Laryngostroboscopy, performed during the luteal phase, showed mild edema of the vocal folds in 6 out of 8 women.

As the literature suggests, estrogen-level alterations cause laryngeal water retention, edema or interstitial tissues and venous dilation.

As estrogen levels begin to decrease, laryngeal tissues begin to absorb water, causing mucosal edema, vascular congestion, and increase vocal fold mass, which can cause a loss of high notes, vocal instability and fatigue, uncertainty of pitch, decreased vocal efficiency and reduced vocal power and flexibility.[93-96]

	GIRBAS	
Patient	**Follicular phase**	**Luteal phase**
TC	12	17
RF	11	13
CR	9	12
TC	9	15
DG	8	10
PL	7	8
TF	6	7
AB	6	7

Table 2 GIRBAS scale: sum of scores of the questionnaire administered for assessment of perceptual voice measures; in the first column the scores in the follicular phase and in the second column in the luteal phase

All patients reported speech emission problems, as can be expected in patients with hearing problems, but only 4 (RF, CR, CT, DG) of these reported a worsening in the luteal phase, with higher scores at perceptual assessment, at the luteal stage. (Tab.2)

Patients reported an increase in vocal fatigue more than an alteration in vocal quality.

Regardless of the phase of the menstrual cycle, spectrographic analysis showed, throughout the sample, a reduction in harmonic frequency extension, more marked in 4 patients. (Fig. 8)

In the recorded vocal segments, the aperiodic component was always represented and was interspersed with harmonics, replacing them in some cases.

This could be the result of irregular glottil vibration due to increased adduction and stiffness of the vocal cords as can be expected in subjects with altered auditory feedback.

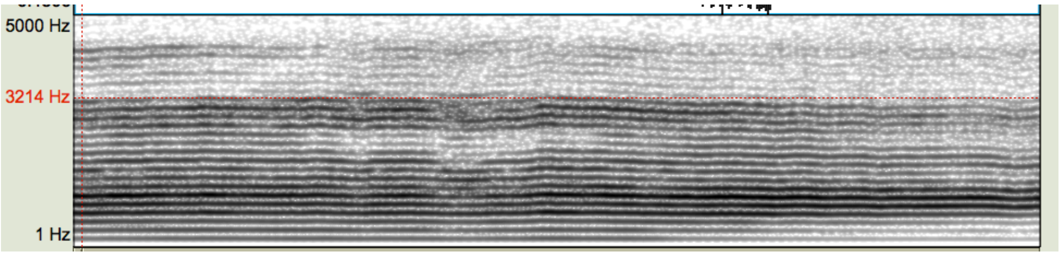


Fig. 8 Example of the reduced frequency extent, in a patient of the sample

The patients(CR DV RF TC), who had inadequate auditory performance, showed greater difficulty in setting the voice and maintaining valid voice parameters.

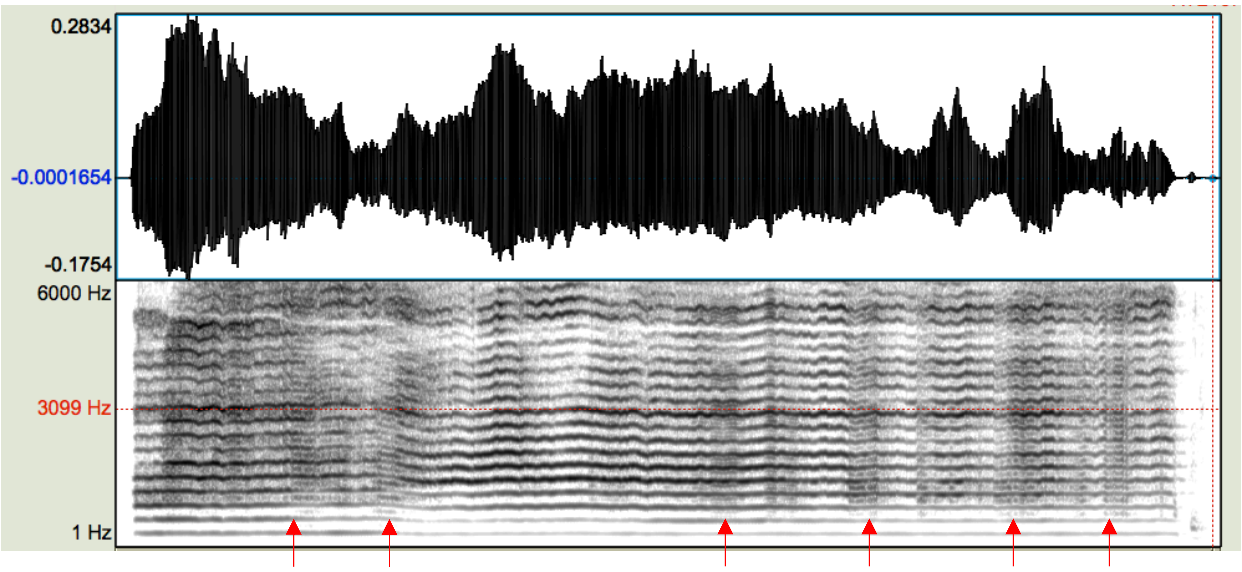


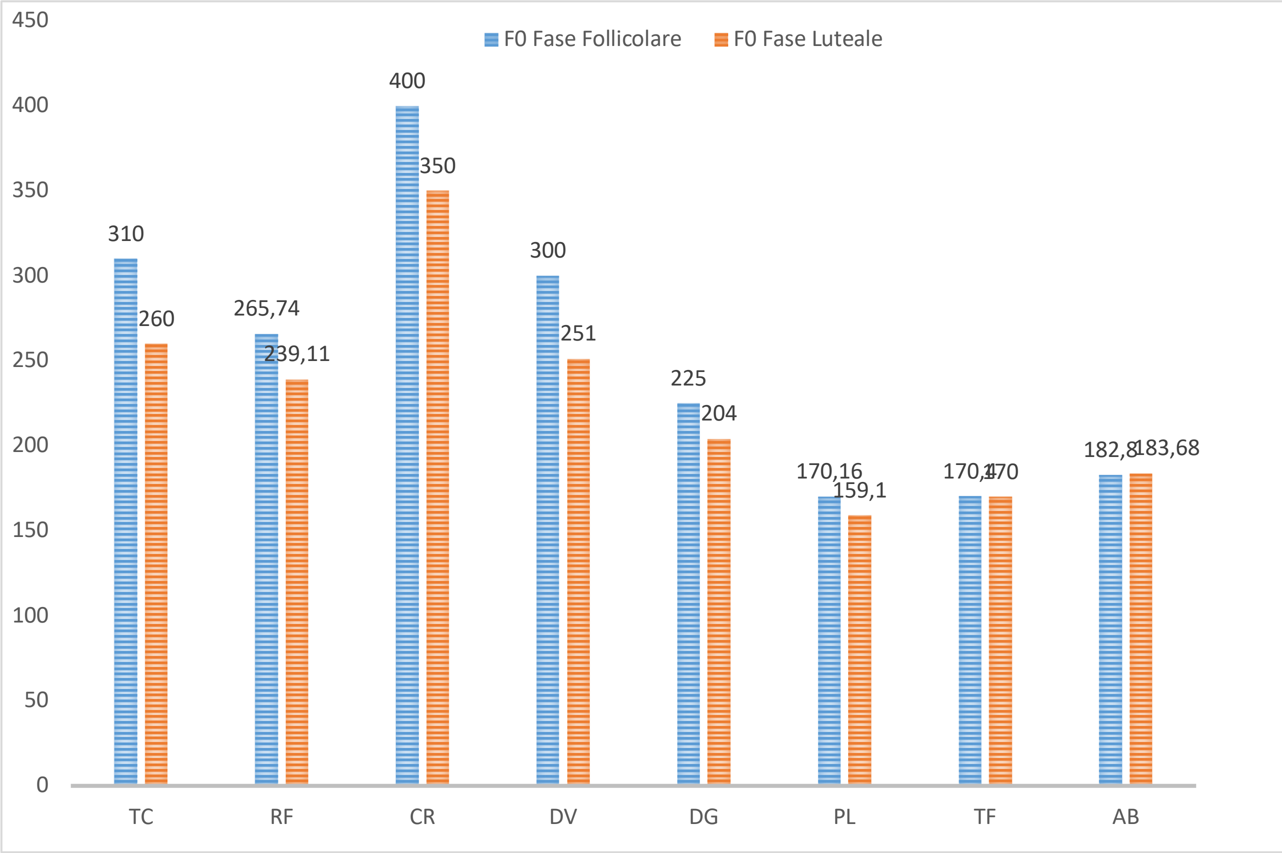
Fig. 9 Presence of interspersed subarmonics to principals components

The irregular vibration of the glottis, in one case (Fig. 9), involved the evidence of multiphonic components, characterized by subarmonics. Graphically, one or more rows with less intensity than the main harmonic components, interspersed with these, and with submultiple frequency of the Fundamental Frequency (F0).

This find is certainly closely related to acoustic feedback.

The voice of the "deaf" is linked to numerous factors (such as the age of hearing impairment onset, the degree of hearing loss, the type of aid used and the prosthetic gain), which make it difficult to define its acoustic characteristics uniquely.

It is clear that the auditory system is an essential component for the development and maintenance of physiological speech quality.



Graph 1 Variation of F0 in the follicular and luteal phase for each patient

Graph 1 shows the variation of the F0 of the sample during the emission of a vowel /a/, in the luteal and follicular phase. Results show that in 6 women there was on average a F0 variation of about 32 Hz between the two phases of the hormonal cycle, with a decrease during the luteal phase. In the remaining 2 patients, however, this value did not change in the two phases of the cycle.

Interestingly, F0 did not change in patients with better IC performance, while those with worse hearing performance showed this variation. (Graph 1)

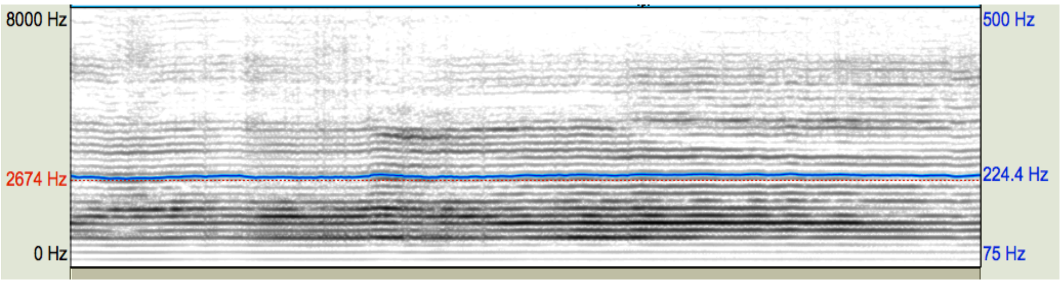


Fig. 10 Example of spectrogram in follicular phase

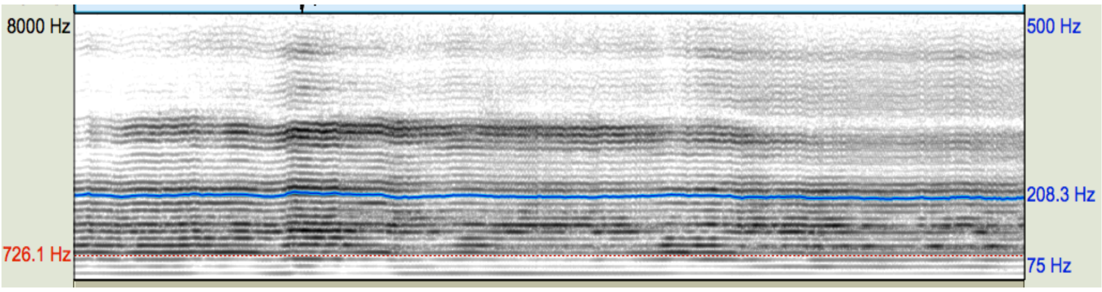


Fig. 11 Example of spectrogram in luteal phase

Our results report that 6 women showed lowering of F0 and the spectral quality of the voice worst in the luteal phase, only 2 showed no significant changes in F0 height to the spectrographic analysis of the voice.

The altered auditory feedback led, particularly in patients with worse auditory performance, to a para-physiological sound mechanics.

There was, in fact, a mismanagement of the subglottic air-flow and of vocal tract resonators, evident in all the recordings made; all patients were post-verbal, so their verbal production was perfectly intelligible but perceptively altered in timbre (predominantly nasal).

To confirm this, the literature suggests that subjects with poor prosthetic functional gain have voice disorders and therefore vocal fatigue. It is reported that in normoacusic women, at the luteal stage, vocal disorders and instrumental correlates are prevalent in subjects with incorrect voice dynamics while they are poorly detectable in euphonic women. [50,51]

Therefore, a person with a cochlear implant, which has acquired the aforementioned para-physiological phonatory mechanism, with alteration of subglottic airflow, muscular tension and a mismanagement of the vocal tract resonators, will be more prone to fatigueal vocal activity, which in luteal phase of menstrual cycle, can promote the onset of relapsing edemas and therefore premenstrual voice variations.

As mentioned above, in support of our data, it is important to remember that the vocal fold contains estrogen, progesterone, and androgen receptors with a similar distribution between sexes.

Hormone receptors allow cell signaling to occur, and the presence of sex hormone receptors in the vocal fold tissue indicates a relationship between hormones and vocal fold functions.[97]

Although both aged men and women experience endocrine function changes resulting in declines in sex hormone production, the dramatic and sudden decline of estrogen production following menopause greatly differs from men's progressive decline of androgens . Therefore, the senescence of the endocrine system may contribute to the sexually dimorphic pattern of vocal aging.[98,99]

Several age-related vocal changes affecting the female voice have been well documented. Morphological changes of the larynx include vocal fold thickening, increased vocal fold edema, and increased prominence of the vocal process.

Following menopause, the vocal folds thicken and become more edematous.[100,101]

About our study, however, it is worth pointing out the critical issues we have faced for voice analysis of patients:

- A small sample for the purpose of a study of the voice, which in itself has countless intra and inter-individual variables
- subjectivity in the judgment of severity of disphony
- difficulty in standardizing the analysis method (choosing the most reliable method among the many available as the type and length of the analysis window, matching the degree of blackening and intensity levels in dB, sampling rate, etc.).

In fact, the assessments made on the spectrographic path are fundamentally semi-objective or entirely subjective, based on a visual judgment.

Our study was based on vowel /a/ analysis, produced by conversational voice, effortlessly, at constant intensity and frequency. The vowels, in fact, are the signals that best reflect the glottic functionality (they are sound phons) and also the resonance effects of the supraglottic vocal tract.

CONCLUSIONS

The work confirmed the role of hormones in corporal homeostasis.

The results showed how, during the luteal phase, the symptoms referred by patients corresponded to precise and objective signs. In fact, in the luteal phases, there were the following findings:

- the vestibular examination confirmed a peripheral labyrinthine suffering attributable to an increase in the cochlear liquids;

- the impedances of the implanted electrodes underwent an increase, probably due to the electrolytic imbalance in the surrounding environment;

- the vocal recognition tests worsened, this result is probably linked to an increase in the electric impedances and the altered central auditory elaboration caused by an estrogenic fall.

- Laryngostroboscopy, showed mild edema of the vocal folds in 6 out of 8 women and in the same 6 patients, acoustic analysis of voice showed lowering of F0 and the spectral quality of the voice worst in the luteal phase

The hormonal changes discussed here occur physiologically in every woman, however, clinical symptoms vary greatly, due to poor objective assessments by the same patients, which are often misunderstood and confused with those associated with other audio-vestibular pathologies.[102]

Clearly, hormones play important roles in auditory processing. Some hormones possess neuroprotective properties (estrogen)via complex cell signaling pathways while others mediate regulation (aldosterone) of cochlear ion channels.[103]

In our study the audio-vestibular symptoms, reported by the patients with the cochlear implant, seemed to be amplified and, in particular, the lessening of their auditory ability is considered very annoying.

Literature has shown the influences of hormonal variations both on the ear and directly on the brain substance.[104,105]
Furthermore, emerging data indicate that estradiol synthesized in the nervous system, plays an essential role in the cerebellar-dependent behaviors and motor memory formation, affecting multiple synaptic plastic sites at the cerebellar and possibly extra-cerebellar networks and it could influence a variety of sensorimotor phenomena depending on cerebellar synaptic plasticity.[104]

These findings are in accordance with our results showing a difficulty in speech recognition tests, probably due not only to the increase in electrical impedance of the IC but also to a difficulty in central language processing.

Vestibular suffering, likewise, seems to be linked to changes in endocochlear fluids[105] and the deterioration of vocal qualities is a mirror of the hydroelectric alteration that occurs throughout the body during hormonal fluctuations.

Specifically, our results, regarding the deterioration of vocal qualities, also seem to be related to vocal tract "malmenage" that is greater in subjects with poor auditory prosthetic recovery.

These patients will be more prone to fatigueal vocal activity which, in luteal phase of menstrual cycle, can promote the onset of relapsing edemas and therefore premenstrual voice variations[57,59].

Overall, it is important to clarify the hormonal influences on hearing in all epochs of life, in order to better understand how the central and peripheral auditory systems are affected. This could allow for better personalized treatment options for patients of all ages.

Thus, it is important to bear in mind everything to avoid negative results during rehabilitation.

In the specific case of premenstrual hormonal fluctuations, it would be indicated (as is done for Meniere's disease) provide a daily note of symptoms, diet, and menstruation, useful for monitoring and treating symptoms. In fact, most patients may have improvements in symptoms with dietary restrictions on sodium and a diuretic cycle.

Appendix

Cochlear Implant

Cochlear implant (IC) is an implantable device that contains one or more sources of current and an array of electrodes implanted in the cochlea: the electric current is used to stimulate nerve fibers. The principle of operation of such device is to translate sounds into electrical signals that, appropriately encoded, stimulate the terminations of the auditory nerve within the cochlea. Electrical stimulation aims to replace the function of hair cells. In general, the IC consists of:

- Microphone, which picks up the beep sound and converts it into an electrical signal;
- Speech processor, which processes the electrical signal;

Transmitting and receiver coil system, which allows communication between the external processor and the internal part, which is surgically implanted inside the skin and receives information from the transmitter.

Electrodes, which stimulate neurons to send information to nerve centers. These electrodes are inserted inside the cochlea.

Fig. 7 Speech Processor.

Modern ICs consist of multiple electrodes (arrays of electrodes), each electrode or electrode pair is associated with a certain band of the sound spectrum (channel) allowing the device to take advantage of the entire tonal map of the auditory system.

The electrodes are placed inside the cochlea and the stimulation of them depends on the frequency of the input signal and is linked to the speech processor processing algorithm.

Fig. 8 Internal coil

You can perform telemetric measurements to determine the correct functioning of the cochlear implant:

Neural Response: An electrode sends the stimulation and the adjacent electrode measures the response of the auditory nerve.

This is able to determine whether electrical stimulation activates neural areas near the stimulation electrode.

Impedance: Test that measures the physical state of the stimulation electrodes, that is, if the electrode is able to stimulate.

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