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E A R L Y MENOPAUSE

Premature Ovarian Failure

Comunichiamo La Salute, Scientific Cultural Association
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This book as an informational purpose only. Every effort was made to make it clear, to date, easily understandable by a wide audience, but we can not exclude possible omissions and errors. Medicine is a science in constant evolution and only your Doctor can explain the peculiarities, prognosis and terapeutical options for your condition.

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Thank you for comments and contributions that could improve future updates. This work is open to collaborations. Last Updated: April 10, 2012

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TARGET AUDIENCE AND GOALS

- Information and support for patients;
- support for general practitioners and specialists in their informing activity;
- early diagnosis and prevention of Premature Ovarian Failure (POF).

INTRODUCTION

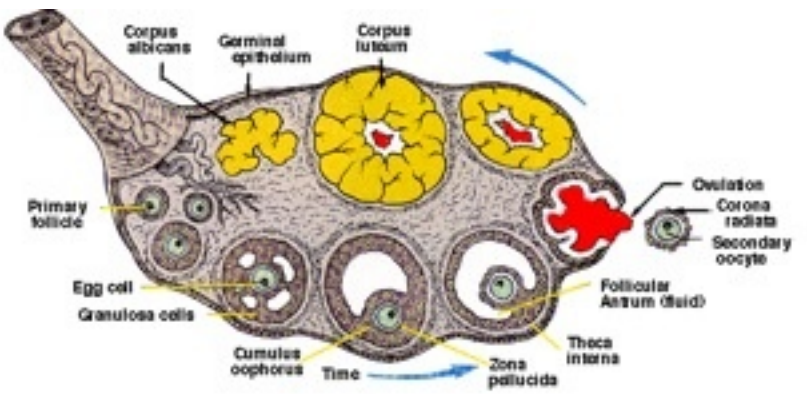
Premature Menopause so called Early Menopause, Premature Ovarian Failure (POF), Premature Ovarian Insufficiency (POI) is one of the most important topics of female reproductive endocrinology and at the same time one of the most controversial and misunderstood issues in modern medicine.

The ovaries are endocrine and reproductive organs localized in the pelvis on both sides of the uterus and close with the tubes; they are nourished by two arteries (ovarian and uterine) and supported by the ovarian and infundibulopelvic ligaments. They have an external structure called cortical, dedicate mainly to the ovarian cycle (follicular grouth) and an internal structure called medullary (vascular and connective component).

They produces mainly estrogens but also androgens, progesterone and other glycoprotein hormones such as Inhibin, Activin and the Follicolostatin and oocytes (female reproductive cells). At the same time, the reproductive function is linked to the oocytes content and maturation:1-2 million germ primordial oocytes are present at birth, but this number is reduced drastically to about 300,000 - 400,000 at the puberty.

These oocytes will allow a normal woman to have about 400 ovulations in their lives (about 13 times a year) in a period known as "reproductive" extending from menarche to menopause.

With menopause, ovulatory function ends; the ovaries reduces their size and their internal structure becomes more compact (uniform); estrogen production falls dramatically.



The ovary is very dynamic during the reproductive life. In this picture you can see what is called the "ovarian cycle".

DEFINITIONS AND EPIDEMIOLOGY

Early Menopause, Premature Menopause, Premature Ovarian Failure (POF), Premature Ovarian Insufficiency (POI) are synonyms for a same clinical condition characterized by the onset of ovarian hormonal and reproductive failure (in variable degrees and sometimes reversibile) in a young woaman before age 40.

There are spontaneous forms (1-3% of general female population) that not correlate to a specific situations and secondary forms or iatrogenic (4-5%) usually resulting from medical (chemotherapy, radiotherapy) or surgical (removal of ovaries) treatments.

The possibility of a spontaneous remissions (often temporary) and the rare possibility of conception indicate the need to clearly distinguish Premature Ovarian Failure from other forms of menopause (ie surgical or physiological menopause) with irreversible estrogen deficiency and reproductive failure.

SYMPTOMS

Menstrual irregularities are the main symptom: usually they starts with the abbreviation of the menstrual cycle (polimenorrea) and progress to secondary amenorrhea (absence of menstruation); but also primary amenorrea (failure of menses to occur by age 16) can correlate with Early Menopause.

Variable degrees of autonomic disturbances (hot flashes, insomnia, irritability) may be present.

Difficulty or inability to conception (infertility) is a very common condition in this patients.

Symptoms may be only partially represented and their sequence in time may sometimes appear intermittently; thereby the diagnosis is not always easy but sometimes difficult and insidious.

Some patients may maintain regular menses and an apparent state of complete wellbeing for many years showing only unexplained infertility.

ETIOLOGY

For most cases it's impossible to identify a specific cause: for such forms defined as primary or idiopathic, genetic factors may play an important role. In many cases it is clear a strong familiar aggregation.

Oocyte depletion (reduced number of oocytes) is probably the pathogenetic mechanism most frequently involved in gonadal dysgenesis and in hypoplasia or aplasia of the Thymus; but an accelerated follicular atresia can occur also in chromosomal diseases affecting mainly the number and structure of chromosomes X (Turner syndrome, premutation FMR1 gene and Fragile X Syndrom), hereditary metabolic enzyme diseases (galactosaemia), some viral infectious (Herpes Zoster, Cytomegalovirus).

Follicular dysfunction is assumed in the forms of spontaneous premature ovarian failure in which follicle growth and ovulation fails to interference of immune, molecular or enzimatic factors despite a normal follicle count.

Within this group are reported all cases associated with Systemic Lupus Eritomatosus, Hascimoto Chronic Thyroiditis, Poliglandular Endocrine Sindrome, Diabetes Type 1, Vitiligo , Sjogren's Syndrome, Rheumatoid Arthritis, Autoimmune Adrenal Insufficiency (Addison's disease). Frequent association with autoimmune diseases makes this ipotesis very suggestive but a direct relationship between immune system and ovarian function has to be proven yet.

Unfortunately we still know very little about Early Menopause and it can not be excluded in many cases concurrent mechanisms of follicular depletion and dysfunction.

DIAGNOSIS

The diagnosis is not always easy and can be misunderstood for many years.

Persistent menstrual irregularities and infertility always require Follicle Stimulating Hormone (a small polypeptide hormone secreted by Pituitary Gland) and 17 beta estradiol (the main ovarian estrogen) assay.

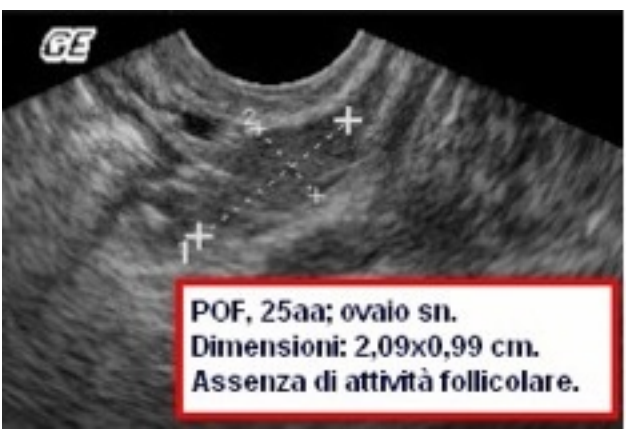
Follicle Stimulating Hormone (FSH) above 10 mIU / ml is suggestive for an initial ovarian failure (subclinical) and greater than 20 mU / ml can be considered diagnostic.

Most important is the correct assessment of FSH and 17 beta estradiol: at least in two separate determinations on the day 3 of the mestrual cycle (any day in amenorrea) are necessary. Pulsatile secretion of FSH require almost thre determinations every 20 '.

Reduction of 17 beta estradiol below 20 pg / ml occurs only in the most "profounds" and clinically evident situations.

Pelvic ultrasound has an important diagnostic role: it could describe volumetric reduction of the ovaries and (little or absent follicular activity) uterus (ipostimulate endometrium).

For most Authors ovarian biopsy is not useful to confirm the diagnosis.



ECT SCAN from a patient (25yo) affected by ovarian insufficiency. Note the absence of follicular activity and reduced gonadal volume.

COMPLEMENTARY INVESTIGATIONS

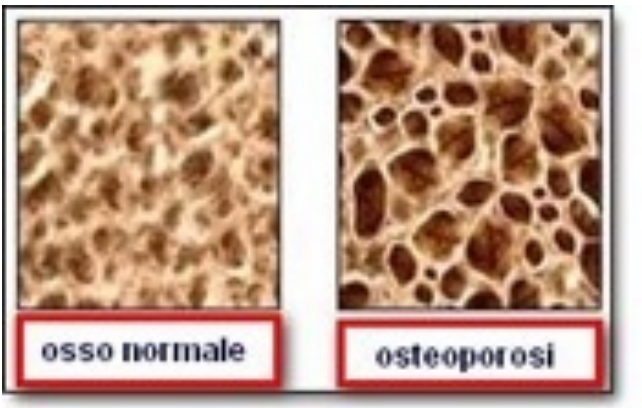
Investigations carried out in possible association with autoimmune endocrine diseases (Thyroid and Surrenal Glands) and some connective diseases should be performed in all subjects.

Karyotype (chromosome investigation) should always be carried out even in apparently healthy women with regular physical and psychosocial development with reproductive success.

Consueling and the genetic FMR1 premutation (X fragile) investigation should always be offered in the presence of family history positive for early menopause, mental retardation or if the patient still has neurological disorders.

Bone Mineral Content evaluation is interesting to evaluate possible osteopenia or osteoporosis as side effects of hypoestrogenism.

Thyroid and Surrene function requires a costant monitoring in this patients.



In this picture note the differences in bone trabecular structure; on the right a typical osteoporotic bone.
The osteoporotic bone has a lower resistance and therefore is more prone to fractures.

DIFFERENTIAL DIAGNOSIS

Differential diagnosi covers all conditions that may determine ipergonadotropic amenorrea (absence of menses with FSH values increased) primary or secondaryand most useful are Inhibin B and Anti Mullerian Hormone (AMH) investigation because directly related to ovarian reproductive and endocrine function.

Assay of ovarian antibodies has not proven useful in clinical practice.

CLINICAL MONITORING

Particular attention should be given to monitoring:
. uro-genital trophism;
. bone calcium content (MOC)
. cardiovascular conditions;
. Thyroid (Hashimoto's Thyroiditis and Secondary Hypothyroidism), adrenal (Addison's disease) and Parathyroid (hypoparathyroidism);
. psychological conditions;
. autoimmune diseases;
. possible side effects of estrogen replacement therapy.

SHORT AND LONG TERM EFFECTS

Consequences at the short term are mainly related to menstrual irregularity and autonomic disturbances (hot flashes, insomnia, emotional instability), the psychological aspects (anxiety, depression) and reproduction (infertility).

In the long term problems are linked to estrogen deficiency: genitourinary tropism abnormalities (vaginal dryness, dyspareunia, perineal altered tone, urinary infection), skin (premature aging), bone (osteopenia, osteoporosis), cardiovascular (ischemic, stroke) and centra nervous system (attention).

In absence of specific interventions reduced performance can affect quality and length of life; some studies have shown an mortality increase risk for all-cause in women with POF.

A delay in diagnosis may therefore result in serious damage to health.

THE REPRODUCTIVE PROBLEM

Reproductive problems are a serious aspects of Early Menopause becouse Infertility occurs in women still very young.

The problem is not only linked to accelerated follicular atresia (quantitative reduction of follicles) but also to a simultaneous deficiency of oocyte quality that even in the presence of ovulation makes fertilization improbable or otherwise abnormal (early abortion).

Spontaneous conceptions are possible but very rare and in many cases eggs donation remains the only concrete solution.

In women at risk it's important to evaluate what is known as "reproductive potential", (probability to ave a normal pregnancy), a complex multifactorial evaluation involving the "ovarian reserve".

For this purpose, in addition to a focus on the "menstrual history", have been proposed static (FSH and 17 beta estradiol on the 3rd day of the cycle) and dynamic tests based on the ovarian response to exogenous stimulation.

Morfovolumetric evaluation of the ovaries associated with antral follicle count has emerged in recent years as a useful and most predictive tool.

SUBJECTS AT RISK AND PREVENTION STRATEGIES

Some risk factors have been identified:
. POF present in family history;
. genetic and metabolic disorders;
. Autoimmune disease;
. Endocrine disorders such as immune-based Type 1 diabetes and Hascimoto Thyroiditis;
. Addison's disease;
. some surgical procedures on the ovaries;
. tubal sterilization.

Their identification should lead to a greater attention on the functionality of the ovary.

The prevention of Secondary Premature Ovarian Failure is possible in some patients candidate to chemioterapy and/or pelvic radioterapy. At this regard there are strategies for "saving the ovaries" involving:
. the use of GnRH Analogues (temporary menopause), oral contraceptives;
. ovarian laparoscopic dislocationlocation.

Wen a rescue is impossible should be considered oocytes or ovarian tissue cryopreservation.

Ovarian damage in many cases is predictable and must always be discussed with the young patients.

DISEASE PROGRESSION

Most cases of premature ovarian failure remain undiagnosed for a long time (hidden forms); in other cases amenorrhea onsets dramatically even whith very intense neurovegetative symptoms such as hot flashes, sweating profuse, insomnia, emotional instability.

A key feature of this disease is still evolving its unpredictability. Some patients have conceived after diagnosis and I have observed two cases of pregnancy occurred in the presence of significant menstrual irregularities (one case was secondary amenorrhoea) and neurovegetative symptoms (hot flashes).

The spontaneous regression occurred during replacement therapy (E/P) are quite frequent (10%), particularly in less serious cases, unfortunately they are not predictable with regard to the time of occurrence and their duration. During the remissions rare cases of spontaneous conception and reproductive success were also described.

Between these two extremes there is a very wide variety of clinical conditions that may even change over time.

On the basis of symptoms, hormonal and reproductive capacity we can identify four clinical stages:

Grade	menses	FSH level	Fertility
1 (occult)	Regular	normal	low
2	Regular	Borderline (<20)	low
3	Irregular	High	Very low
4	Absent	High	absent

Unfortunately until now there is no international classification of different stages of this disease.

THERAPY

Therapy that can restore normal ovarian function does not exist at the moment; some experimental trayals are started recently; then the main objective is avoiding effects of estrogen deficiency and ensure a normal length and quality of life for these patients.

Estroprogestins terapy is the standard for this patiens, mainly in the sequential-cyclic administration to' mantein regular witdrawal menses.

Therapeutic intervention is mandatory in presence of neurovegetative symptoms and menstrual irregularities

Of course, before starting these drugs contraindications should always be excluded.

The estrogen progestin replacement therapy will be continued if possible until the time of physiological menopause (50 years).

Ovulation induction therapy should be considered only for limited time and for reproductive goal with a permissive ovarian reserve. Their use is still very controversial.

RECENT EVIDENCES AND PERSONAL CONTRIBUTIONS

Our original scientific papers suggest a possible role of cigarette smoking in determining an early menopause in women who are otherwise normal; therefore it can not be excluded that smoking can also lead to disease progression in women with premature ovarian failure.

We also noted the increasingly early onset of menopause in patients with endometriosis, especially when previously treated for operating laparoscopic ovary. This evidence was the subject of a report in the literature and will be confirmed by further studies and consistent.

CONCLUSIONS AND RECOMMENDATIONS

Premature Ovarian Failure (POF), Early Menopause, Premature Ovarian Insufficiency (POI) certainly is one of the most important endocrine diseases.

Unfortunately its diagnosis is often late with sometimes serious consequences for the young patients.

It's necessary to conduct a large information about this problem.

Identification of patients at risk is possible and prevention can be evaluated in some cases.

Every unexplained infertility or abnormal menstrual rhythm needs to be checked for ovarian failure.

From the same Author:

Gynecology Explained to Women

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