

Polycystic Ovary Syndrome Therapy

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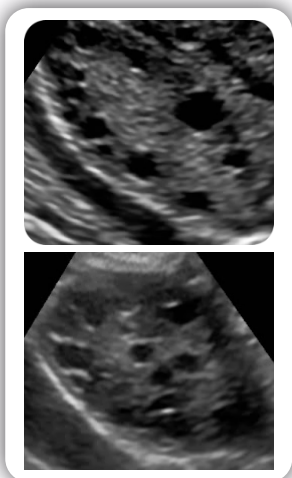


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¿ What is an ovulatory dysfunction ?

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>>> POLYCYSTIC OVARY SYNDROME (PCOS)



Ovulatory dysfunction
caused by
HYPERANDROGENEMIA

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>>> PCOS

OVULATORY DYSFUNCTION

Three or more abnormal cycles in a year, or two, consecutive abnormal cycles.

Abnormal cycles mean

- SHORT CYCLES: <24 days
- LONG CYCLES: > 36 days
- NORMAL LENGTH CYCLES (between 24 to 36), with a short luteal phase or its absence.

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¿ What is hyperandrogenemia ? ¿ How to make a good diagnosis ?

Total Testosterone

0.15 – 0.98 nM/L¹

< 40 ng/dL²

Miller K, Rosner W. et al. (2004)
Salmi D, Zisser H, Jovanovic L. (2004)

HYPERANDROGENEMIA V/S HYPERANDROGENISM

Mass spectrophotometry

RIA

ELISA

Other Symptoms

- Oily skin and hair
- Acne
- Mood changes
- Hirsutism
- Obesity
- Infertility
- Menstrual Irregularities (80%)

It should be noted that PCOS is **NOT** characterized by:

- An abrupt beginning.
- Short-term symptomatology (less than one year).
- Sudden and rapidly progressive hirsutism.
- Occurring after the third decade of life.
- No family history of PCOS.
- Virilization signs: frontal alopecia, clitoromegaly, hoarse voice, highly muscle development.

TYPES

- DHEA-S
- Androstenedione
- Total Testosterone
- Free Testosterone
- 17 OH progesterone

POLYCYSTIC OVARY SYNDROME

Polycystic Ovarian Syndrome (PCOS) is the most frequent hormonal and metabolic disease in women.

15-18%

- (1) Lobo R, Annals of Intern Med, 2000
(2) Ben-Rafael Z, C O Obstet and Gynecol, 2000
(3) Dunaif A, The Am J of Med, 1995

- **Functional adrenal hyperandrogenemia**
 - Premature adrenarche, dysregulation/exaggerated adrenarche, congenital adrenal hyperplasia, hyperprolactinemia, abnormal cortisol action or metabolism.
- **Functional gonadal hyperandrogenemia**
 - Functional ovarian hyperandrogenism (extraovarian virilizing disorders, ovarian steroidogenic block, dysregulation of P450c17), intersex.
- **Peripheral androgen over production**
 - Obesity, idiopathic.
- **Tumoral hyperandrogenemia**
 - Adrenal tumors, ovarian tumors, gonadotropin-secreting tumors.

PRECOCIUS PUBERTY V/S PRECOCIUS OVULATION

It is the stage in which there is a high secretion of **steroidal hormones** (adrenal and gonadal), producing the obvious signs of reproductive maturation such as **breast development** and the appearance of **facial hair**.

Vigil P et al (2011) J Pediatr Adolesc Gynecol 24:
330-337

- Adrenarche
- Maturation of the hypothalamic-pituitary-gonadal axis
- Gonads maturation

- Increase of adrenal **androgen levels** (DHEA, DHEA-S y androstenediona).
- It starts around 6 to 7 years old until 13 to 14 years old.
- The development of pubic and axillary hair begins.

PCOS AND INSULIN RESISTANCE

¿ Are all the women with PCOS obese ?

NO !

Prevalence of obesity in different PCOS populations according to studies carried out in centers in Santiago, Chile; Pennsylvania, USA; New York, USA

Origin of the PCOS population	PCOS criteria for diagnosis	Percentage of patients with overweight
Santiago 76 women (Vigil, 2000)	Ovulatory dysfunction and hyperandrogenemia	31.2% BMI >26
Pennsylvania 280 women (Legro, 2001)	Chronic an ovulation and hyperdogenism	87.5% BMI>26
New York (Dunaig, 1987)	Chronic an ovulation and hyperdogenism	60% obese > 20 % overweight

Vigil P., Cort

DETECTION OF GLUCOSE METABOLISM DISORDERS USING OGTT WITH INSULIN, IN REPRODUCTIVE-AGED PATIENTS.

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ABSTRACT

Context

High prevalence of glucose metabolism disorders (GMD) such as glucose intolerance (GI) and insulin resistance (IR) exist in women with reproductive diseases. Diagnosis of GMD is generally done through the HOMA index, Oral Glucose Tolerance Test with insulin (OGTT-I) with two points (0 and 120 min) or five points (0, 30, 60, 90, and 120 min).

Objective

To compare the detection of GMD through Homa index, two and five points OGTT-I.

Methods

Five-points OGTT-I conducted after 10 hour fasting and calculation of HOMA index.

Patients

430 reproductive-aged women with ovulatory dysfunction.

Intervention

Five-points OGTT-I.

Main Outcome Measures

Glucose and insulin obtained from blood samples. Subjects were classified regarding the presence/absence of GMD according to the HOMA index, and interpretation of two- and five points OGTT-I, according to the American Diabetes Association standards.

Results

HOMA index estimates less altered subjects (4.9%, $p < 0.01$) than two points OGTT-I (33.7%), which are lower than estimates from five points OGTT-I (48.6%, $p < 0.01$). Regarding IR, five points OGTT-I estimates the highest percentage (31.6%), followed by two points OGTT-I (25.6%), and the HOMA index (4.8%). Regarding GI, five points OGTT-I estimated a higher percentage of altered subjects (31.8%) than two points OGTT-I (17.4%).

Conclusions

The use of five points OGTT-I detects 14.9% more GMD altered subjects than two points OGTT-I ($p < 0.01$) and 43.7% more than the HOMA index ($p < 0.01$). Also, five points OGTT-I detects 6% more subjects with IR than two points OGTT-I ($p < 0.10$) and 26.7% more than the HOMA index ($p < 0.01$). Two points OGTT-I can detect 20.7% more IR subjects than the HOMA index ($p < 0.01$). With respect to GI five points OGTT-I detects 14.4% more altered subjects than two points OGTT-I. The analysis of glucose and insulin from the five points OGTT-I allows better distinction of different GMD (IR, IG or IR+IG) than two points OGTT-I or the HOMA index.

OUT OF 10 WOMEN WITH OVULATORY DYSFUNCTION

HOMA test detects 0.5 women with GMD



A two points OGTT-I (0 and 120 min) detects 3 women with GMD



A five points OGTT-I (basal, 30, 60, 90 and 120 min) detects 5 women with GMD



Do all PCOS patients have insulin resistance ?

THUS,

INSULIN RESISTANCE



HYPERINSULINEMIA



OVARIAN HYPERANDROGENIC STATE



FOLLICULAR INVOLUTION

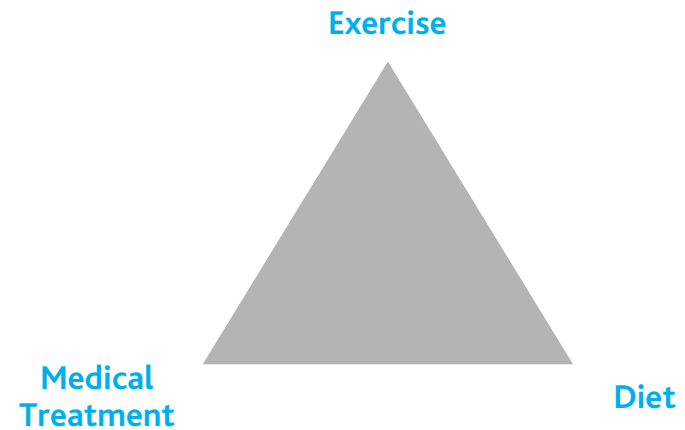


OVARIAN CYST FORMATION



OVULATORY DYSFUNCTION

What can be done ?



- Improve insulin resistance
- Decrease testosterone levels

1. Combination E+P pills
2. Androgen blockers
3. Insulin sensitizers
4. A combination of the above

(Geller et al., 2011)

TREATMENT MODALITIES

PCOS

Therapy	Mechanism of action	Regular menses	↓ Androgens levels of effects	Improves insulin sensitivity	Contraception	Metabolics effects
Combination E+P pills	Endometrial changes	✓✓	✓		✓	May be associated with worsened lipid profile, hypertension, decrease glucose tolerance and prothrombotic effect
	↓ GnRH frequency					
	↓ LH, FSH					
	↑ SHBG					
	↓ free androgens					
Androgen blockers	↓ androgen action	✓	✓	✓		May be associated with improved lipid profile and
Weight loss ± insulin sensitizers	↑ insulin sensitivity		✓			Associated with improved glucose tolerance, lipid profile and blood pressure
	↑ SHBG					
	↓ free androgens					

Geller, D. H., Pacaud, D., Gordon, C. M., & Misra, M. (2011)

BCP

TREATMENT

POLYCYSTIC OVARY SYNDROME

Hormone	Condition	Treatment
↑ Testosterone	PCOS	Dexamethasone Estro-progestatives Finasteride Cyproterone acetate Spironolactone Flutamide
↑ Insulin	PCOS-IR	Metformin TZD (Rosiglitazone - Pioglitazone) Inositol Vidagliptin - Sitagliptin - Saxagliptin Liraglutide Empagliflozin - Dapagliflozin

PROS AND CONS

INSULIN SENSITIZER

PROS

Reduces insulin resistance and addresses an important component of the pathophysiology of PCOS

Useful for treating hyperglycemia in patients with PCOS-associated type 2 DM

Metformin may cause weight reduction and is associated with improvement in lipid profile

Potential for use in adolescents with lean PCOS in whom lifestyle modification is likely to be ineffective

Excellent safety profile for metformin, with few side effects reported

An option in patients with Factor V Leiden mutations and other risk factor for coagulopathy in whom E+P combination pills may be contraindicated

Geller, D. H., Pacaud, D., Gordon, C. M., & Misra, M. (2011)

CONS

Insulin-sensitizing effect may not persist after discontinuing medication

Weight reduction is minor with metformin; TZDs may cause weight gain and peripheral lipogenesis

Cosmetic improvements may be less marked than with E+P combination pills

Insulin sensitizers may induce ovulation, risk of unwanted pregnancy unless used with contraception

Insufficient studies of efficacy and long term safety of insulin sensitizers in adolescents

Higher incidence of gastrointestinal disturbance

Geller, D. H., Pacaud, D., Gordon, C. M., & Misra, M. (2011). State of the art review: emerging therapies: the use of insulin sensitizers in the treatment of adolescents with polycystic ovary syndrome (PCOS). *International journal of pediatric endocrinology*, vol(1), 1-19.

- Upregulates the insulin receptor.
- Participates in the regulation of intracellular and extracellular calcium.
- Modulates immune response. Hypovitaminosis D may induce inflammatory response, which is associated with insulin resistance.
- Modulates ovarian steroidogenesis. Increases expression of CYP19, 3- β -hydroxysteroid dehydrogenase and production of progesterone, estradiol and estrone.

(Lerchbaum & Obermayer-Pietsch, 2012)

- Obesity contributes to reduced levels of vitamin D, probably as a consequence of the sequestering of VD by the adipose tissue.
- Obese patients are exposed 57% less to the sun than non-obese patients, which would add another factor contributing to low vitamin D levels.

(Lerchbaum, E. & Obermayer-Pietsch, B., 2012)

Article

Ovulation, a sign of health

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The concept of the ovarian continuum can be understood as a process that occurs during a woman's lifetime and begins during intrauterine life with fertilization. Women start their reproductive years with approximately five hundred thousand follicles containing oocytes, of which only around five hundred will be released during ovulation. Ovulation has been recognized as an event linked with reproduction; however, recent evidence supports the role of ovulation as a sign of health. The use of biomarkers that help women recognize ovulation enables them to identify their health status. This knowledge helps medical healthcare providers in the prevention, diagnosis, and treatment of different pathologies related with endocrine disorders, gynecological abnormalities, autoimmune, genetic, and neoplastic diseases, as well as pregnancy-related issues. The knowledge of the ovarian continuum and the use of biomarkers to recognize ovulation should be considered a powerful tool for women and medical professionals.

Summary: The ovarian continuum is a process that occurs during a woman's lifetime. It begins during intrauterine life with fertilization and ends with menopause. This process can be greatly affected by different conditions such as changes in hormonal levels and illnesses. Therefore, understanding and promoting the knowledge and use of biomarkers of ovulation in women is a key aspect to consider when evaluating their health status. The knowledge and education about the ovarian continuum should be taken into account as a powerful tool for women and medical professionals.

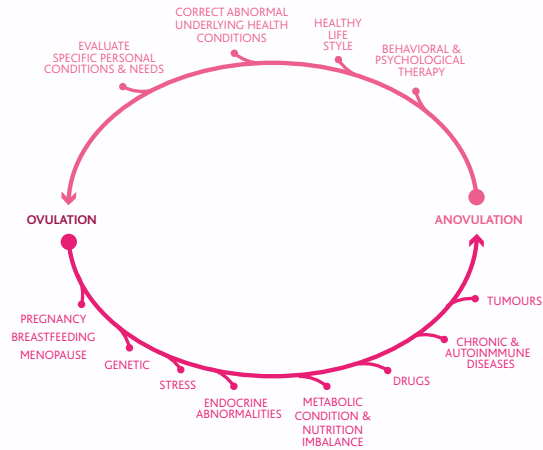
Keywords: Ovarian continuum, Women's health, Ovulation, Biomarkers

INTRODUCTION

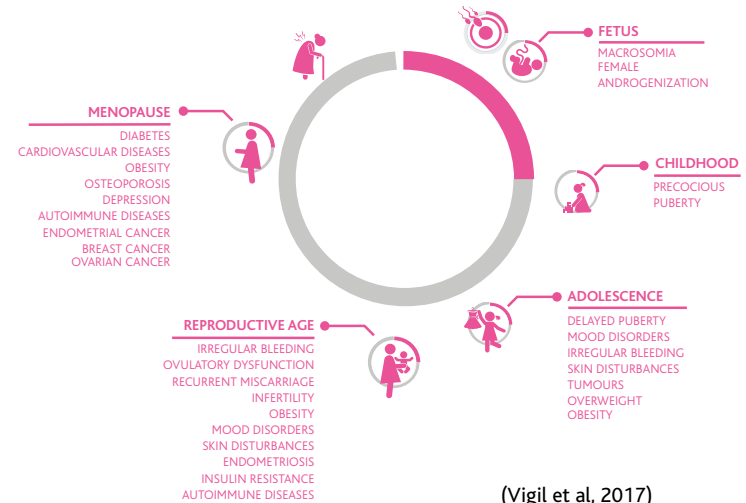
The concept of the ovarian continuum can be understood as a process that occurs during a woman's lifetime and starts during intrauterine life (Brown 2011). This continuum begins with fertilization. Two months later the primordial germ cells leave the embryo to avoid differentiation and migrate to the yolk sac, where they remain for four weeks. After this time, they are found in the gonadal ridge where they are surrounded by somatic cells.

to organize (Motta, Malabe, and Nottola 1997), and around seven million primordial follicles are formed in the ovaries, but only one to two million remain at birth (Block 1952). The rest of the primordial follicles degenerate via an apoptotic process called follicular atresia. Later on during her reproductive life, a woman will ovulate around five hundred oocytes (Lunenfeld and Insler 1993).

Often, healthcare providers have focused on regularizing bleeding patterns, without



(Vigil et al, 2017)



(Vigil et al, 2017)

- Hyperandrogenemia is the common denominator for a group of disorders called PCOS.
- It is imperative to use an appropriate lab for the diagnosis of hyperandrogenemia and to assist in the management and follow up of the patient.
- Our current knowledge is quite adequate to institute credible diagnostic procedures and a personalized therapy.
- It must be defined with the patient whether or not she wants to recover her ovulation knowing that this is a sign of health for her.

If you want more information about the class, papers, suggestions, questions...

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Thanks!

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