24° CONGRESSO NAZIONALE
A.Gi.Co.
Sindrome dell'ovaio policistico
e disturbi metabolici della menopausa:
due facce della stessa medaglia?

19-21 Ottobre 2022

Grand Hotel Excelsior
REGGIO CALABRIA

PCOS e infertilità

Stefano Palomba

Ospedale Sant'Andrea, Roma
Università degli Studi di Roma «Sapienza»

SAPIENZA
UNIVERSITÀ DI ROMA

Premise

PCOS

Oligo-anovulation

Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome

Daniel A. Dumesic, Sharon E. Oberfield, Elisabet Stener-Victorin, John C. Marshall, Joop S. Laven, and Richard S. Legro

Department of Obstetrics and Gynecology (D.A.D.), David Geffen School of Medicine at UCLA, Los Angeles, California 90095; Division of Pediatric Endocrinology (S.E.O.), Children's Hospital of New York-Presbyterian, Columbia University College of Physicians and Surgeons, New York, New York 10032; Department of Physiology (E.S.-V.), Karolinska Institutet, 171 77 Stockholm, Sweden; Center for Research in Reproduction and Division of Endocrinology (J.C.M.), Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia 22903; Division of Reproductive Medicine (J.S.L.), Department of Obstetrics and Gynecology, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands; and Department of Obstetrics and Gynecology (R.S.L.), Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033

Dumesic et al., Endocr Rev 2015

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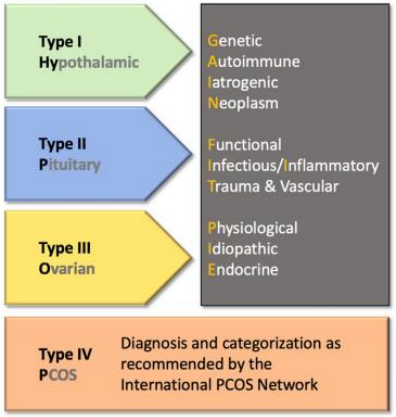
PCOS diagnosis and new classification of ovulatory disorders

FIGO Ovulatory Disorders Classification (HyPO-P)



Graphical depiction of the proposed FIGO Ovulatory Disorders Classification System. *Note:* After the individual is diagnosed with an ovulatory disorder, the core or first level of the system is the allocation to type I, II, or III disorders according to their presumed primary source: hypothalamus, pituitary gland, or ovary, respectively. PCOS comprises the type IV category and the criteria proposed by WHO are to be used to determine this categorization. The second level stratifies each anatomic category (types I–III) into the known or presumed mechanism according to the "GAIN-FIT-PIE" mnemonic as appropriate and applicable. Abbreviation: PCOS, polycystic ovary syndrome.

Human Reproduction, pp. 1–19, 2022
https://doi.org/10.1093/humrep/deac180

human reproduction ORIGINAL ARTICLE *Reproductive endocrinology*

The FIGO Ovulatory Disorders Classification System†

Malcolm G. Munro [1,*,‡], Adam H. Balen[2,‡], SiHyun Cho[3], Hilary O.D. Critchley[4], Ivonne Diaz[5], Rui Ferriani[6], Laurie Her
Edgar Mocanu[8], and Zephne M. van der Spuy[9]; for the FIGO Committee on Menstrual Disorders and Related Health Impa
and FIGO Committee on Reproductive Medicine, Endocrinolo
and Infertility

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Korea [4]The University of Edinburgh, Edinburgh, UK [5]Nueva Granada University, Bogota, Colombia [6]The University of
Paolo, Brazil [7]Centre Hospitalier Universitaire Liège, University of Liège, Liège, Belgium [8]Trinity College, Dublin, Ireland [9]
Cape Town, Cape Town, South Africa

ARTICLE IN PRESS

SPECIAL ARTICLE

The FIGO Ovulatory Disorders Classification System

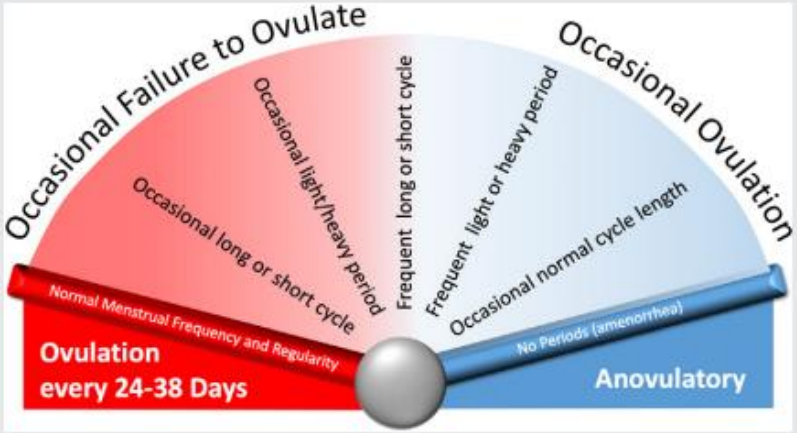
Malcolm G. Munro,[a] Adam H. Balen,[b] SiHyun Cho,[c] Hilary O. D. Critchley,[d] Ivonne Díaz,[e] Rui Ferriani,[f] Laurie Henry,[g] Edgar Mocanu,[h] and Zephne M. van der Spuy[i] for the FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility

[a] The University of California, Los Angeles, Los Angeles, California, USA; [b] The University of Leeds, Leeds, UK; [c] Yonsei University, Seoul, South Korea; [d] The University of Edinburgh, Edinburgh, UK; [e] Nueva Granada University, Bogota, Colombia; [f] The University of São Paolo, São Paolo, Brasil; [g] Centre Hospitalier Universitaire Liège, University of Liège, Liège, Belgium; [h] Trinity College, Dublin, Ireland; and [i] The University of Cape Town, Cape Town, South Africa

7. The Rotterdam criteria should be used to define PCOS?
Mean score (1–9): 6.7
Disagree (%): 22.0
Neutral (%): 12.2
Agree (%): 65.9

Munro et al., Fertil Steril 2022
Munro et al., Hum Reprod 2022

Ovulatory disorders as infertility factor in women with PCOS



Disorders of ovulation exist on a spectrum that ranges from occasional failure to ovulate to chronic anovulation. *Note:* Typically, but not always, these disorders manifest abnormalities in menstrual parameters such as frequency, regularity, duration, and volume of bleeding, and, in the case of chronic anovulation with amenorrhea. It is apparent that the luteinized unruptured follicle (LUF) and luteal out of phase (LOOP) disorders exist on a similar spectrum of varying frequency.

Ovulatory disorders may range from those that are isolated, intermittent, or chronic.

Munro et al., Fertil Steril 2022
Munro et al., Hum Reprod 2022

PCOS

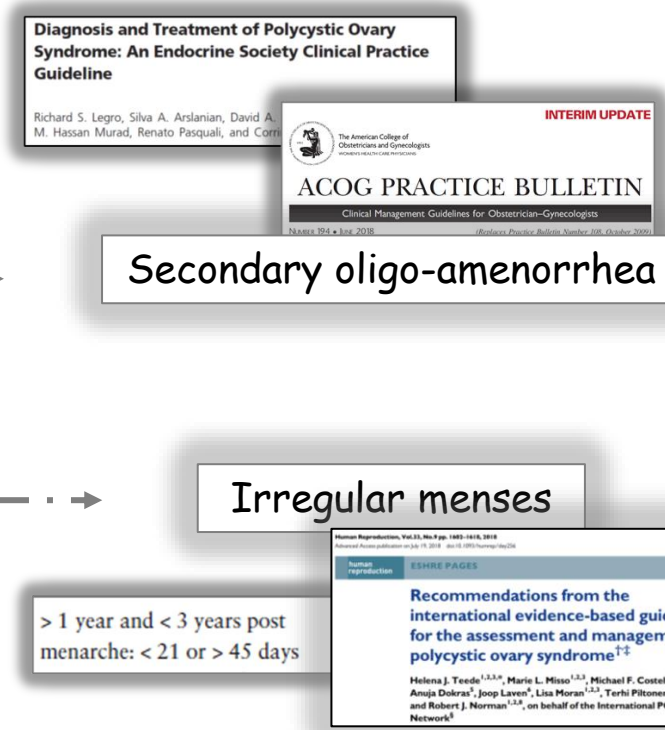
Fertility impairment

Oligo-anovulation

Secondary oligo-amenorrhea

Irregular menses

> 1 year and < 3 years post menarche: < 21 or > 45 days



Legro et al., J Clin Endocrinol Metab 2013
ACOG Committee on Practice Bulletins – Gynecology, Obstet Gynecol 2018
Teede et al., Hum Reprod 2018

PCOS: diagnostic criteria, features and phenotypes

Signs and Symptoms*	National Institutes of Health Criteria† 1990 (both are required for diagnosis)	Rotterdam Consensus Criteria 2003‡ (two out of three are required for diagnosis)	Androgen Excess Society§ 2006 (hyperandrogenism plus one out of remaining two are required for diagnosis)
Hyperandrogenism‖	R	NR	R
Oligoamenorhhea or amenorrhea	R	NR	NR
Polycystic ovaries by ultrasound diagnosis		NR	NR

Abbreviations: R, required for diagnosis; NR, possible diagnostic criteria but not required to be present.
*All criteria recommend excluding other possible etiologies of these signs and symptoms and more than one of the factors present to make a diagnosis.
†Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston (MA): Blackwell Scientific Publications; 1992.
‡Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fertil Steril 2004;81:19–25.
§Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterwelt W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. Androgen Excess Society. J Clin Endocrinol Metab 2006;91:4237–45.

Legro et al., J Clin Endocrinol Metab 2013
ACOG Committee on Practice Bulletins – Gynecology, Obstet Gynecol 2018

Human Reproduction, Vol.36, No.9, pp. 2421–2428, 2021
Advance Access Publication on August 1, 2021 doi:10.1093/humrep/deab181

human reproduction **OPINION**

Is fertility reduced in ovulatory women with polycystic ovary syndrome? An opinion paper

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Submitted on December 06, 2020; resubmitted on June 22, 2021; editorial decision on July 12, 2021

Are PCOS women with ovulatory phenotypes sub-fertile?

Are PCOS women who ovulate under treatment sub-fertile?

Unsolved questions about subfertility in PCOS

Are PCOS women with ovulatory phenotypes sub-fertile?

Head-to-head comparison between non-ovulatory patients with and without PCOS

Are PCOS women who ovulate under treatment sub-fertile?

Head-to-head comparison between patients with PCOS who ovulate under treatment and ovulatory women without PCOS

Palomba, Hum Reprod 2021

Fertility data in women with PCOS

More frequent request of infertility consultations
More frequent ART procedures
Older and more likely to be nulliparous at the time of delivery

Roos et al., 2011; Hart and Doherty, 2015; Rees et al., 2016; Mills et al., 2020

Probability of a first childbirth 20% lower when considering total pregnancies and 40% lower considering only spontaneous pregnancies, with a time-to-first childbirth after spontaneous conception 2 years longer

Persson et al., 2019

Same number of children at the end of the reproductive span

Hudecova et al., 2009

Similar prevalence for at least one child

Chen et al., 2020

High efficacy of IVF treatments

Heijnen et al., 2006; Sha et al., 2019; West et al., 2014; Chen et al., 2020

High efficacy of infertility treatments especially for women of advanced maternal age

Kalra et al., 2013

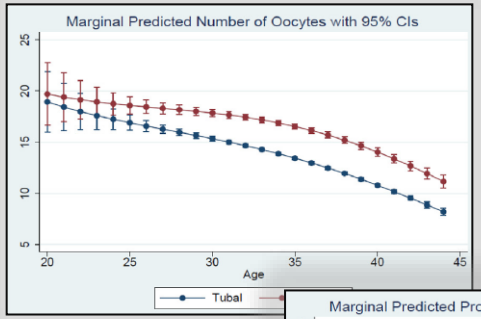
Fertility rates restored at all ages after the diagnosis

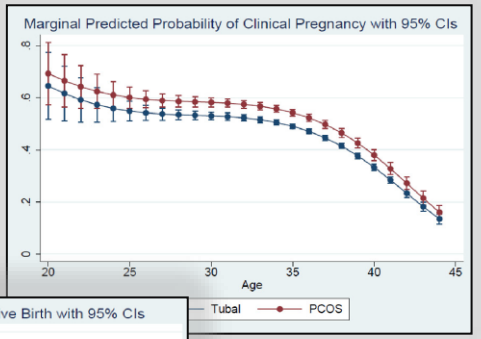
Rees et al., 2016

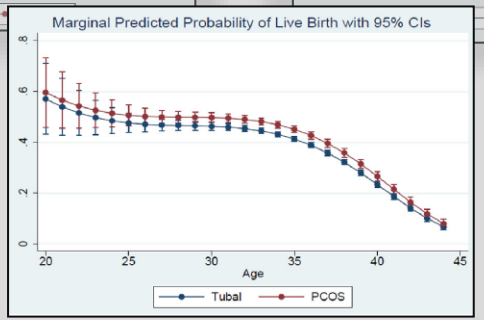
Better reproductive IVF performance in PCOS patients: relationship with extended fertile window

IVF treatment characteristics in women with tubal factor infertility and PCOS.

	Tubal	PCOS	*P* value
Total IVF cycles	27,870	16,416	
No. of oocytes retrieved	12.8	16.4	<.001
No. of cryopreserved embryos, mean ± SD	5.1 ± 4.3	6 ± 5.1	<.001
Subjects with cryopreserved embryos, %	33.8	42.4	<.001
Implantation rate, %	21.3	27.5	<.001
Clinical pregnancy rate per cycle start, %	35.8	42.5	<.001
Miscarriage rate, %	17.4	16.6	<.001
Live-birth rate per cycle start, %	29.1	34.8	<.001
Pregnancy plurality, %			NS
Singleton	66.3	65.3	
Twin	31.1	32.2	
Higher order multiple pregnancy (≥triplet)	2.6	2.5	

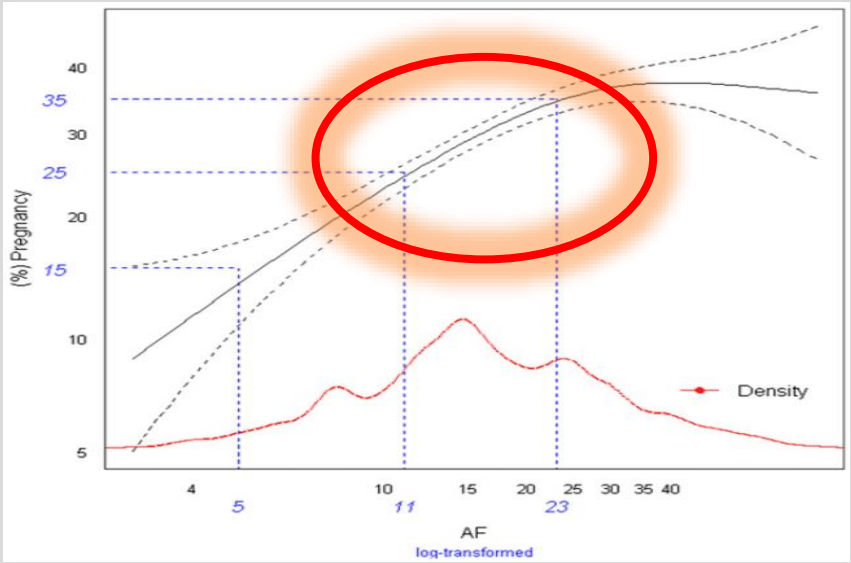






Kansal Kalra et al., Fertil Steril 2019

Effect of antral follicle count (AFC) on pregnancy rate

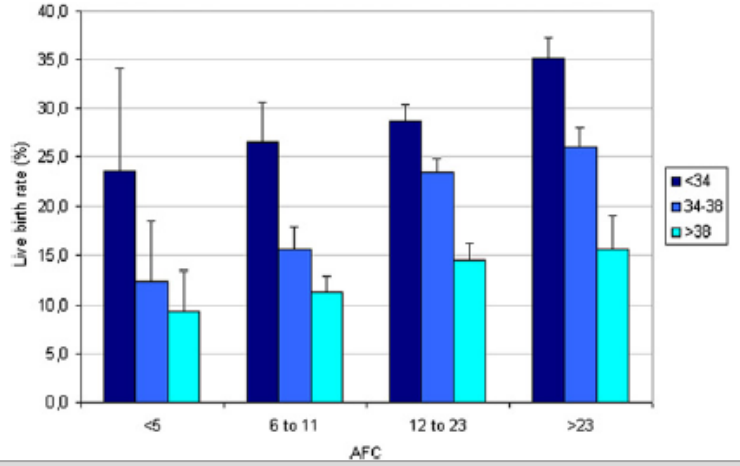


High AFC = PCOM!

Holte et al., Fertil Steril 2011

Effect of AFC on live birth rate per oocyte pickup

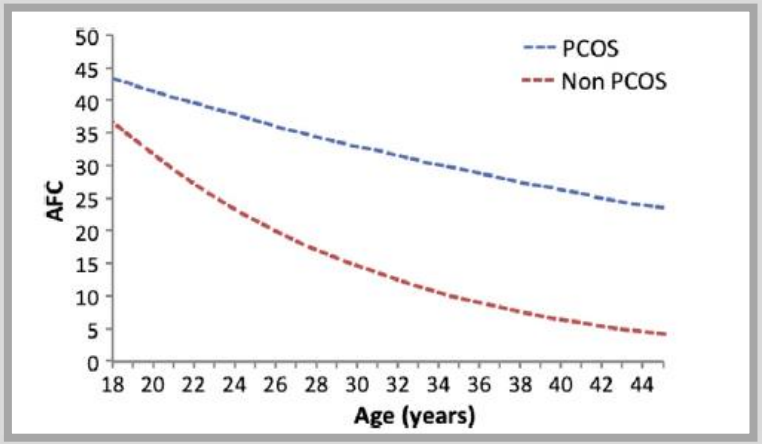
Live-birth rates/oocyte pickup (%) relative to different ages at oocyte pickup (<34; 34–38; >38 years) within each antral follicle count-stratum (<5, 6–11, 12–23, and >23 antral follicles). Mean values ± standard error of the mean. N = 4,004 IVF-ICSI treatment cycles. AFC = antral follicle count.

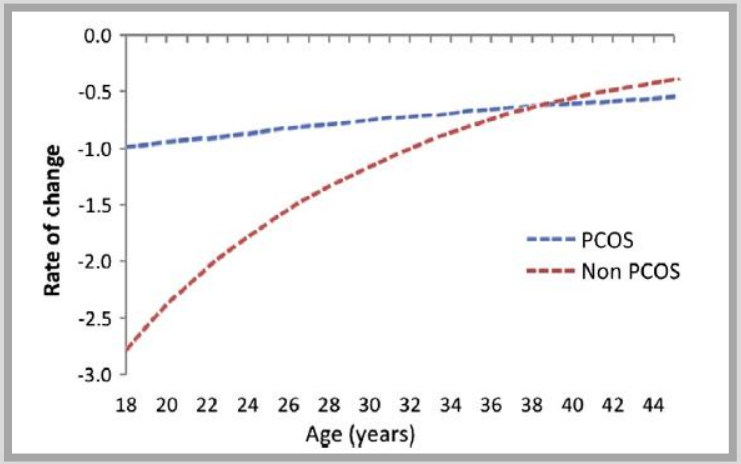


No difference in pregnancy (*P*=0.76) and live-birth (*P*=0.95) rates was observed between ovulatory and anovulatory women.

Holte et al., Fertil Steril 2011

Age-related normogram for AFC in PCOS patients





Wiser et al., Reprod Biomed Online 2013

Pregnancy outcomes in women with PCOS

Human Reproduction Update, Vol.21, No.5 pp. 575–592, 2015
Advanced Access publication on June 27, 2015 doi:10.1093/humupd/dmv029
human reproduction update

Pregnancy complications in women with polycystic ovary syndrome

Stefano Palomba[1,*], Marlieke A. de Wilde[2], Angela Falbo[1], Maria P.H. Koster[2], Giovanni Battista La Sala[1,3], and Bart C.J.M. Fauser[2]

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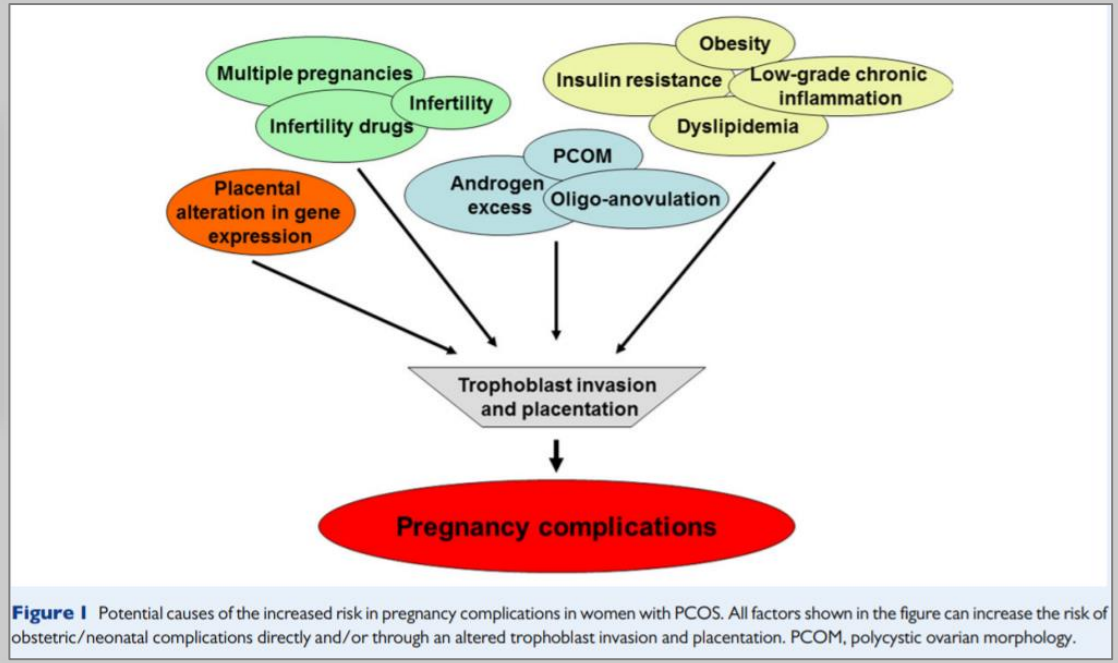


Figure 1 Potential causes of the increased risk in pregnancy complications in women with PCOS. All factors shown in the figure can increase the risk of obstetric/neonatal complications directly and/or through an altered trophoblast invasion and placentation. PCOM, polycystic ovarian morphology.

Palomba et al., Hum Reprod Update 2015

PCOS-related cofactors and subfertility

Obesity and glucose metabolism impairment are associated with an increased time to achieve pregnancy, impaired fecundability

Lim et al., 2019; Oostingh et al., 2019

An increased BMI is closely related to poor reproductive outcomes in both the general and IVF populations

Oostingh et al., 2019; Sermondade et al., 2019

Livebirth rates are even lower when obesity is associated with PCOS

Oostingh et al., 2019

Metabolic syndrome is also associated with a longer time to achieve pregnancy and infertility in general populations that is independent of obesity and IVF

Grieger et al., 2019; He et al., 2019

The relative risk of infertility reported in the literature is likely lower than that observed outside the clinical trial setting because PCOS is closely related to several conditions that are related to infertility!

Palomba, Hum Reprod 2021

Oocyte quality and competence in PCOS

Neuroendocrine and endocrine data

Genomic data

Metabolic alterations: abnormal intrafollicular glucose (energy deficiency) and lipid (free fatty acids) metabolism regulation

Increased intra-follicular oxidative stress (excessive production of reactive oxygen species, ROS) and inflammatory markers (closely related to low-grade chronic inflammation)

Abnormal cross-talk between developing oocytes and surrounding somatic cells during folliculogenesis

Increased incidence of:

- meiotic abnormalities
- alterations of oocyte morphology
- alterations of granulosa cell function
- alterations in expression and function of membrane receptors
- aberrant expression of short and long non-coding RNAs
- alterations of several biomolecules with regulatory functions in oocyte development (including growth factors, cytokines, deaminases, metalloproteases, hormones, adipokines, and lipidases)

Palomba et al., Trend Endocrinol Metab 2017

Biomarkers expression in PCOS oocyte

Biomolecules	Physiological function of marker	Changes reported in PCOS
EGF family	Stimulates cumulus cell expansion and improves nuclear and cytoplasmic maturation of oocytes from MI to MII	Lower FF levels
FGF family	Physiological regulators of FSH action in GCs and TCs	Contradictory data on serum and FF levels
IGF family	Regulates folliculogenesis	Higher FF levels
Neurotrophin growth factor family (NGF, BDNF)	Plays a fundamental role in folliculogenesis and cytoplasmic competence	Higher FF levels
TGF-β family (AMH, GDF9, BMP15, and others)	Under different conditions promotes or blocks folliculogenesis and/or differentiates GC–oocyte complexes	AMH: higher serum and FF levels GDF9, BMP15: contradictory data on serum and FF levels
VEGF family	Plays an important role in angiogenesis, follicular vascularization, and intrafollicular oxygenation	Lower FF levels in women following GnRH antagonist administration; otherwise, higher FF levels
Cytokine family (ILs, TNF-α, sFAS)	Regulates follicle maturation	ILs: lower FF levels TNF-α: higher FF levels sFAS: lower serum levels
Melatonin	Antioxidant against oxidative stress caused by ROS, with varied functions in follicular development; minimizes atresia, improves oocyte maturation, reduces intrafollicular oxidative damage; FF levels of melatonin are threefold higher than in serum	Lower FF levels
ADA1	Modulates the metabolism and recycling of intra-FF adenosine, which plays a crucial role in oocyte survival, growth, and maturation	Controversial data in FF
ADAMTS-1	Matrix metalloproteinase secreted by GCs of relevant importance for expansion of the COC during the ovulation process	Lower FF levels
Leptin	Secreted by adipocytes and can inhibit folliculogenesis, dysregulate GnRH release, and alter ovarian steroidogenesis	Controversial data in serum and FF
DHEA-S	Derives from the catalysis of DHEA and crucial for estrogen production by GCs as these hormones enhance the oscillation frequencies of Ca^{2+} spikes within the oocyte and generate the Ca^{2+} waves necessary for oocyte maturation	Higher serum and FF levels
Hsp27	Antiapoptotic factor	Downregulated in ovarian tissue
ROS	Promotes oocyte maturation and, near the time of ovulation, breakdown of the follicular compartment	Higher serum and FF levels
Lipids	Important for GCs steroidogenesis	Altered FF levels; higher triglycerides, LDL, and VLDL and lower HDL
ZP4	Mediates the interaction between the oocyte and spermatozoa at the zona pellucida by inducing the acrosome reaction of spermatozoa for oocyte cytoplasm invasion; once successful, ZP4 inhibits other spermatozoa from binding synergistically with the ZP3 glycoprotein	Lower ovarian expression in phenotype B

Abnormal expression of biomarkers in PCOS involved in folliculogenesis and steroidogenesis, and interaction oocyte-spermatozoa.

Palomba et al., Trend Endocrinol Metab 2017

Abnormalities of oocyte morphology in PCOS

Table 3. Abnormalities of Oocyte Morphology [8]

Extracytoplasmic
Abnormal or fragmented first polar body
Abnormal zona pellucida
Large perivitelline space
Exogenous material in perivitelline space
Abnormal shape of oocyte
Intracytoplasmic
Excessively granular cytoplasm
Presence of one or more vacuoles
Presence of vacuole-like structures (smooth endoplasmic reticulum disks)

Palomba et al., Trend Endocrinol Metab 2017

Embryo quality and competence

Data on time-lapse analysis

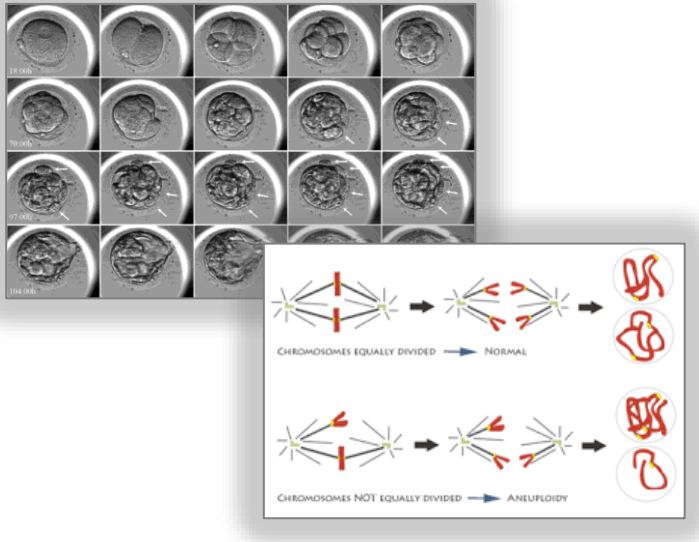
Significant temporal delay for pronuclei breakdown, first cleavage, and three-, four-, and seven-cell cleavages

Wissing et al., 2014

Data on embryonic/fetal aneuploidy

Higher incidence of chromosomal aneuploidies, assessed using single nucleotide polymorphism array analysis, in miscarriages following successful IVF cycles, even after multivariate analysis

Li et al., 2019



Palomba et al., Trend Endocrinol Metab 2017
Palomba, Hum Reprod 2021

Endometrial quality and competence in PCOS

Human Reproduction Update, Vol.27, No.3, pp. 584–618, 2021
Advance Access Publication on December 10, 2020 doi:10.1093/humupd/dmaa051
human reproduction update

Endometrial function in women with polycystic ovary syndrome: a comprehensive review

Stefano Palomba [1,*], Terhi T. Piltonen [2], and Linda C. Giudice [3]

[1]Unit of Obstetrics and Gynecology, Grande Ospedale Metropolitano of Reggio Calabria, Reggio Calabria, Italy [2]Department of Obstetrics and Gynecology, PEDEGO Research Unit, Medical Research Center, Oulu University Hospital, University of Oulu, Oulu, Finland [3]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA, USA

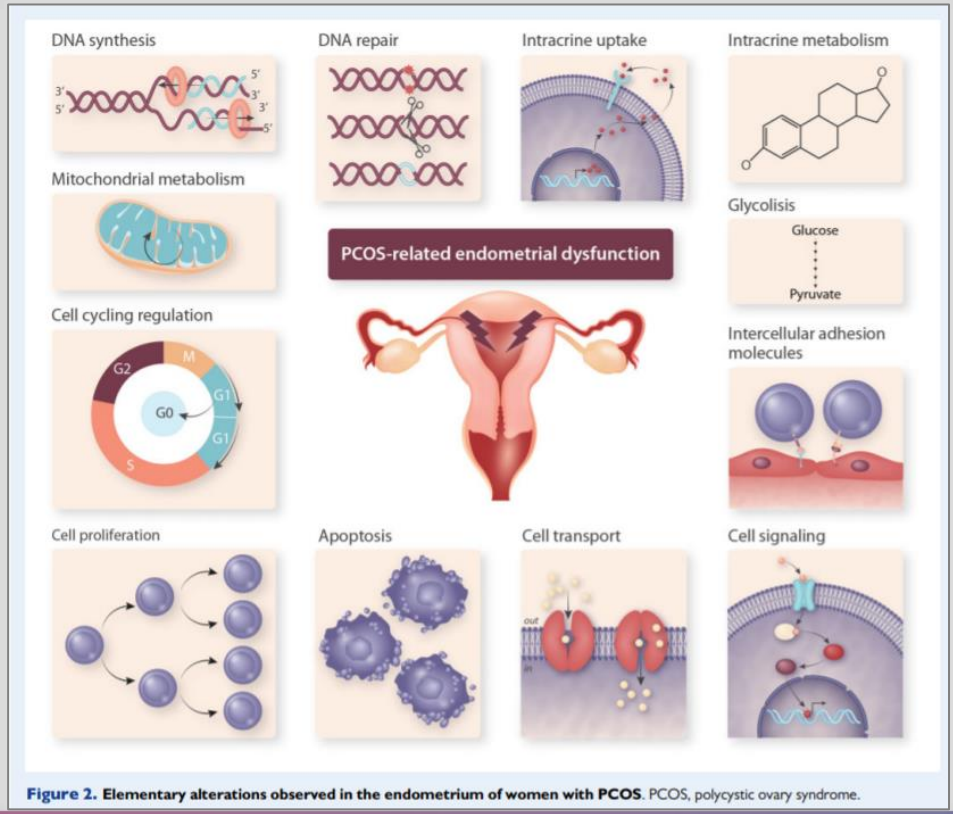


Figure 2. Elementary alterations observed in the endometrium of women with PCOS. PCOS, polycystic ovary syndrome.

Primary endometrial alterations in PCOS

Aberrant expression of sex-hormones receptors

- Enhanced ERα expression
- Suppressed total PR expression
- Enhanced PRα and suppressed PRβ expression
- Aberrant PRα/PRβ isoforms expression
- Aberrant PR function
- Enhanced AR expression

Aberrant expression of sex-hormone receptors coregulators

- Enhanced TIF2 and AIB1 ER coactivators expression
- Enhanced GP-ER ER coactivator expression
- Downregulation of GRP-78 ER coregulator
- Downregulation of MUC1 PR coregulators expression
- Downregulation of PGRMC1 and 2 PR coregulators expression
- Enhanced AR coactivators (AIB1, intermediary factor-2, p-160, ARA70, MAGEA11)

Abnormal regulation of enzymatic pathways

- Downregulation of 17β-HSD expression
- Upregulation of HSD type I expression
- Upregulation of sulfatase activity
- Downregulation of sulfotransferase activity
- Upregulation of 5α-reductase
- Upregulation of 3β-HSD type 2 expression
- Increased HSD type1/type 2 ratio

Abnormal regulation of metabolic pathways

- Increased conversion of E1 to E2
- Increased conversion of DHEA to androstenediol
- Increased conversion of T to DHT
- Reduced expression and function of InR, InR-S1, InR-S2, and IGF-BP1
- Reduced expression and function of the glucose transport pathways (GLUT-4, GLUT-1, GLUT-12, AS160, and MEF-2A)
- Decreased activation of the PI3K/Akt pathway

Palomba et al., Hum Reprod Update 2021

Secondary endometrial alterations in PCOS

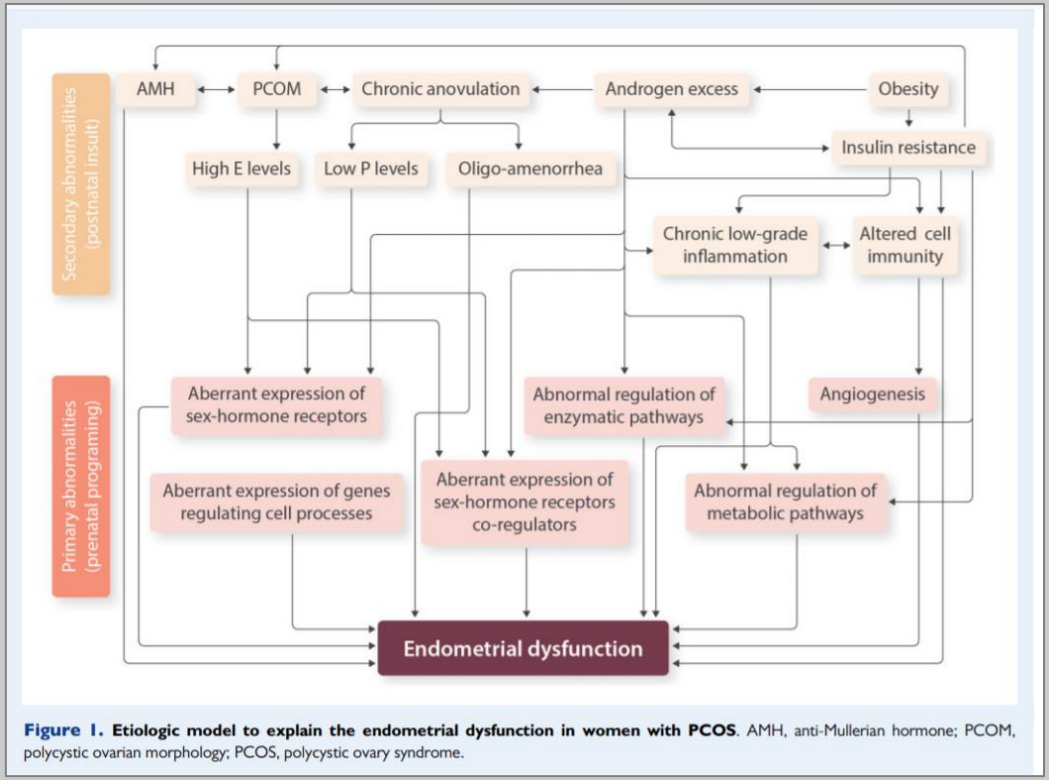
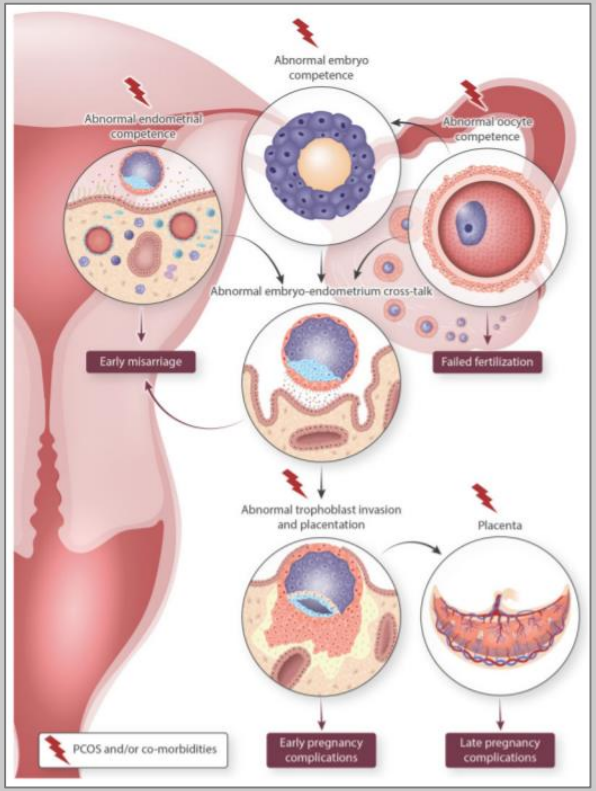


Figure 1. Etiologic model to explain the endometrial dysfunction in women with PCOS. AMH, anti-Mullerian hormone; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

Conclusions



Clinical and experimental data support the hypothesis that women with PCOS are sub-fertile irrespectively from ovulation.

Many factors may contribute to reduce fertility potential in women with PCOS altering the implantation and the trophoblast invasion and placentation.

The fertility treatments are highly effective in women with PCOS.

The correct and immediate diagnosis is crucial for long-term reproductive outcomes.

Grazie per l'attenzione!!!