Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence

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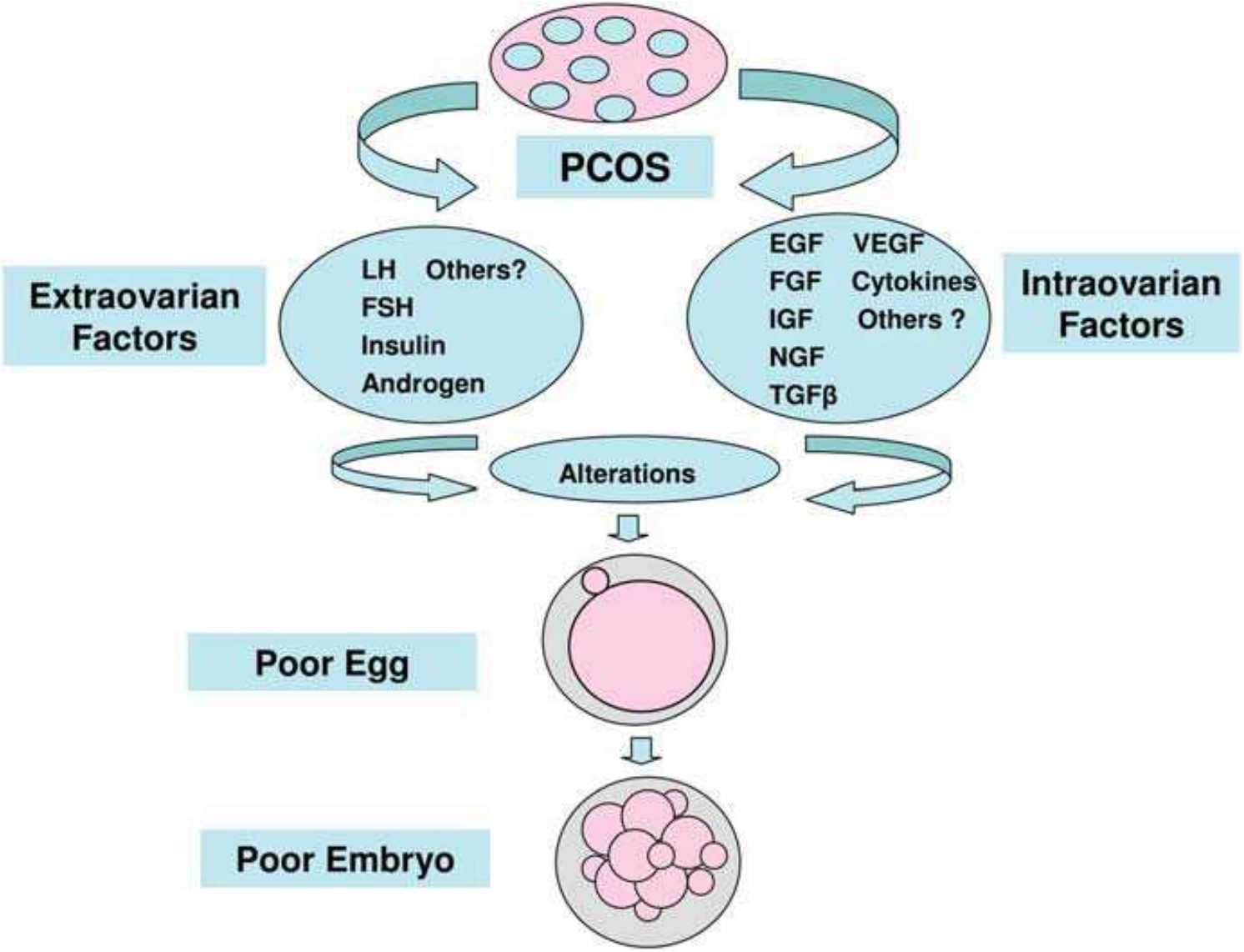
Introduction

- PCOS:
  - hyperandrogenism, hyperinsulinemia, hypersecretion of LH, menstrual dysfunction, hirsutism, infertility and pregnancy and neonatal complications
  - increased number of oocytes (poor quality) → lower fertilization, cleavage and implantation rates, and a higher miscarriage rate

- abnormal endocrine/ paracrine factors, metabolic dysfunction and alterations in the intrafollicular microenvironment during folliculogenesis and follicle maturation is possibly linked with PCOS
- a better understanding of how PCOS is related to abnormalities in extra- and intra-ovarian factor (Fig. 1)


PCOS
Extraovarian Factors
LH Others?
FSH
Insulin
Androgen
EGF VEGF
FGF Cytokines
IGF Others ?
NGF
TGFβ
Intraovarian Factors
Alterations
Poor Egg
Poor Embryo

Methods

- MEDLINE (1950 to January 2010) and GOOGLE for all full texts and/or abstract articles published in English
- This search resulted in 1596 papers.
- Upon screening the results for applicable titles and/or abstracts, only articles correlating to PCOS and its relatives were selected for this review.

Extra-ovarian factors

- Human folliculogenesis and follicle maturation process can be disrupted by abnormal extra-ovarian endocrine factors, resulting in ovarian dysfunction.

(FSH deficiency)

- FSH stimulates follicular growth and recruitment of immature follicles from the ovary.
- FSH is the major survival factor during folliculogenesis
- Human antral follicles between 2 and 5 mm become responsive to FSH
- 6 and 8 mm acquire aromatase activity and potentially increase the estradiol (E2) levels

- With the concomitant rise in E2 and inhibin B, FSH levels then decline in the late follicular phase → only the most advanced and mature follicle is selected to proceed to ovulation.
- At the end of the luteal phase → slight rise FSH level → to initiating the next ovulatory cycle
- PCOS : lower serum FSH levels
- FSH deficiency results in an increased accumulation of antral follicles between 2 and 8 mm → premature arrest and failed to become the dominant follicle

- Recovery of immature oocytes followed by in vitro maturation (IVM) is a potentially useful treatment option for women with PCOS-related infertility.
- the cumulative pregnancy rate by IVM treatment in women with PCOS is comparable with that of other PCOS women undergoing conventional IVF

(Hypersecretion of LH)

- Women with PCOS typically have tonic hypersecretion of LH during the follicular phase of their cycles
- High LH levels → significant decreases in oocyte maturation and fertilization rates, and impaired embryo quality → impaired pregnancy rates, higher miscarriage rates
- suppress FSH function → abnormal GC function (premature GC luteinization and follicular atresia in small antral follicles) → impair the quality of both oocyte and embryo

- damaging the oocyte nucleus → activate premature meiotic processes → apoptosis via a receptor-coupled signal transduction system
- Disruption of the endocrine control of meiosis → impaired extrusion of the first polar body → compromise the chromosomal normality of oocyte → embryonic aneuploidy in women with PCOS

(Hyperandrogenemia)

- Direct increases of ovarian production or an inhibition of hepatic synthesis of sex hormone-binding globin in PCOS with insulin resistance → Elevated free circulating levels of bioactive androgen
- Increased androgen concentrations in the follicular fluid (FF) are associated with elevated serum LH levels → block dominant follicle development and cause follicular arrest and degeneration

- Further studies : elevated testosterone (directly or indirectly) decreases the rates of IVM, fertilization and embryonic development
- The mechanism of testosterone activity within the oocyte may be related to decreased calcium oscillations → inhibiting oocyte cytoplasmic maturation, with effects on meiotic maturation
- elevated testosterone concentrations are associated with higher miscarriage rates in women with PCOS (van der Spuy and Dyer, 2004) → androgens may have a detrimental effect on folliculogenesis and endometrial function

(Hyperinsulinemia)

- Metformin is administered to reduce fasting insulin, LH and free testosterone level, in an effort to restore menstrual cyclicity and fertility
- It has been reported that insulin resistance is related to an increased miscarriage rate

Intra-ovarian factors

- Oogenesis is profoundly dependent upon intra-ovarian factors, in particular follicle fluid factors (FFFs), which are positively related to levels of these factors in serum (Table I).
- Recent studies suggest that the main FFFs implicated in polycystic ovary folliculogenesis are members of the growth factor families, cytokines, inhibins and others

Table I Factors in serum and follicular fluid of patients with PCOS: impact on quality of oocyte and embryo, fertilization and outcome of pregnancy.

Factors	Serum level	FF level	Oocyte quality	Fertilization rate	Embryo quality	Pregnancy rate	References
Activin	↓	↓					Norman et al. (2001), Erickson et al. (1995)
Anti-Müllerian hormone	↑	↑	↑ or ↓	↑ or ≈ or ↓	↑ or ≈	↑ or ≈	Fallat et al. (1997), Wang et al. (2007a, b), Mashiach et al. (2010), Desforges-Bullet et al. (2010)
Epidermal growth factor		↑					Volpe et al. (1991), Almahbobi et al. (1998), Artini et al. (2007)
Fibroblast growth factor	↓ or ↑	↓ or ↑	≈ or ↓	≈	≈		Hammadeh et al. (2003), Artini et al. (2006)
Follistatin	↑	↑					Erickson et al. (1995), Norman et al. (2001), Bdar-Geva et al. (2001)
Brain-derived neurotrophic factor		↑					Johnstone et al. (2008), Buyuk and Seifer (2008)
Bone morphogenetic protein-15		↑	↑	↑	↑		Wu et al. (2007a, b)
Estradiol	↓	↓	↓	↓	↓		Berker et al. (2009), Amato et al. (2003)
Follicular fluid meiosis-activating sterol		↑	↑	≈	≈		Bokal et al. (2006)
Growth differentiation factor-9		↓	↓				Zhao et al. (2010)
Hom[illegible]	↑	↑	↓	↓	↓		Nafee et al. (2010), Berker et al.

Table I *Continued*

Factors	Serum level	FF level	Oocyte quality	Fertilization rate	Embryo quality	Pregnancy rate	References
Superoxide dismutase	↓ or ≈	↓ or ≈					Sabatini et al. (2000), Bausenwein et al. (2010)
Total antioxidant capacity	↓	↓	↓	↓	↓	↓	Chattopadhayay et al. (2010)
Testosterone	↑	↑	↓				Brzynski et al. (1995), Teissier et al. (2000)
Tissue inhibitor of metalloproteinase-1 & 2		↓ or ≈					Lahav-Bratz et al. (2003), Shalev et al. (2001)
Tumor necrosis factor α	↑	↑	↓	↓	↓	↓	Amato et al. (2003), Wu et al. (2007a, b), Kim et al. (2009)
Vascular endothelial growth factor	↓ or ↑	↓ or ↑	↓	↓ or ≈	↓	↓	Bokal et al. (2004, 2005, 2009), Artini et al. (2006, 2009)
Visfatin	↑	≈					Plati et al. (2009)

All data are as compared with controls (patients without PCOS). ↑, increases or positive impact; ↓, decreases or negative impact; ≈, similar; blank, no data.

(Epidermal growth factor → EGF)

- a soluble growth factor → regulation of cell growth, proliferation and differentiation when bound to its receptor, EGFR
- In the human ovary, EGF is found in the FF, regulating follicular development and oocyte meiotic maturation competence via EGFR signaling transduction system in the cumulus cell (CCs)

- EGF inhibits estrogen synthesis in GCs → blocks antral follicle growth and results in follicular arrest in PCOS patients

- Therefore, it is hypothesized that a disruption in the regulatory mechanisms of EGF synthesis and/or physiological function mediated by EGFR may cause anovulatory infertility in women with PCOS

(Fibroblast growth factor family)

- Fibroblast growth factors (FGFs) expressed in GC and theca cells of growing follicles → physiological regulators of FSH action
- FGF levels in the serum and FF are lower in PCOS patients in comparison to patients with endometriosis and tubal factors
- In contrast, another research group: FGF concentrations are increased in the FF and serum of PCOS patients when compared with controls
- Therefore, FGF alterations in the FF and serum remain controversial

(Insulin-like growth factor family)

- Insulin-like growth factors (IGFs) are multifunctional polypeptides with insulin-like activity.

- This complex system consists of
  - two surface-receptors (IGF1R and IGF2R)
  - two receptor ligands (IGF-I and IGF-II)
  - six high-affinity IGF binding proteins (IGFBP 1-6)

Insulin-like growth factor-I/II and IGF binding proteins

- IGFs and their binding proteins, IGFBPs, have important regulatory functions in ovarian follicular development
- Circulating IGFs are produced in the liver, local IGF-I is secreted by theca cells whereas IGF-II is synthesized by GCs
- One recent report: the FF IGF-I levels in PCOS women are elevated, although IGF-II and IGFBP-1 levels are lower than NOW

- In infertile IVF patients, the ratio of IGF-1/IGFBP-1 in the serum and FF is significantly increase in women who become pregnant, highlighting the importance of oocyte quality and maturity during ovarian stimulation for IVF
- Results from in vitro culture models demonstrate that IGF-I can significantly increase embryonic development and blastocyst formation

(Neurotrophin growth factor family)

- Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), NT-3 and NT-4/5 are major members of the neurotrophin (NT) family of growth factors that are involved in development of the central and peripheral nervous systems
- NTs play a fundamental role in folliculogenesis and cytoplasmic competence of the oocyte
- Evidence from some studies: increased FF BDNF and NGF levels are closely related to the pathology of women with PCOS

(Transforming growth factor-b family)

- transforming growth factor (TGF)-b family play an important biological role in follicle growth and oocyte development.
- These family members include anti-Mullerian hormone (AMH)/Mullerian inhibiting substance (MIS), activin, follistatin, inhibins, bone morphogenetic protein (BMP)-9 and growth differentiation factor (GDF)-9

Anti-Mullerian hormone/Mullerian inhibiting substance

- It inhibits the development of the Mullerian ducts in the male embryo
- expressed by GCs within ovaries of women of reproductive age, controlling the formation of primary follicles by inhibiting excessive follicular recruitment by FSH
- reflect some aspects of ovarian function, making AMH levels a potential marker for assessing conditions such as PCOS and premature ovarian failure

- Women with PCOS have elevated serum and FF AMH levels → associated with increased development of antral follicles and follicular arrest in PCOS patients

- Recent complementary investigation suggests that increased FF AMH in women with PCOS may have harmful consequences on oocyte quality and maturation

Activin, follistatin and inhibin

- FS : regulate growth and differentiation; over-expression → increased arrest of follicular development and decreased oocyte developmental competence
- Activins : secreted by smaller follicles, promoting follicular development by increasing the GC response to FSH stimulation, decreasing androgen synthesis and enhancing oocyte maturation.
- Inhibins : produced by the dominant follicle → stimulate theca cell androgen production for E2 synthesis
- Increased FS/activin ratios are well known contributors to the pathophysiology of PCOS →activin enhancing post-fertilization development, and FS blocking this function
- Elevated inhibin B levels are closely related to an elevated risk of developing PCOS

Growth differentiation factor-9 and bone morphogenetic protein-15

- GDF-9 and BMP-15 (also called as GDF-9b) are highly expressed in growing and full grown oocytes
- play fundamental roles in regulating CC functions through the processes of mitosis, proliferation, apoptosis, luteinization, metabolism
- In infertile women, elevated FF BMP-15 levels are positively correlated with improved oocyte quality and higher rates of fertilization and embryonic development → a good indicator of oocyte maturity and fertilization ability

(Vascular endothelial growth factor family)

- In the ovary → expressed in GCs and theca cells
- plays an important role in angiogenesis, follicular vascularization and intrafollicular oxygenation
- In vitro culture studies show that VEGF stimulates the maturation of bovine oocytes during IVM, resulting in increased rates of fertilization and embryonic development

- In women with PCOS, elevated FF VEGF is closely associated with the development of ovarian hyperstimulation syndrome
- An opposing study concluded that follicles containing higher FF VEGF concentrations provide better MII oocytes, compared with those with lower FF VEGF concentrations
- Therefore, FF VEGF may serve as a dynamic indicator for the evaluation of follicular maturity, subsequently predicting oocyte maturity, fertilization success and embryo development in PCOS patients

(Cytokine family)

- the family comprises the interleukins (IL1 35), leukemia inhibitory factor, tumor necrosis factor (TNF)a, soluble Fas (sFas) and sFas ligand (sFasL) (TNF subfamily).
- In PCOS patients cytokines are believed to play a role in ovarian hyperstimulation and hyperandrogenism

Interleukins

- Studies have elucidated that ILs, namely IL-1, IL-2, IL-6, IL-8, IL-11, IL-12 and other cytokines, play multiple roles in folliculogenesis, ovulation and corpus luteum function
- FF IL-12 levels vary within immature and pre-ovulatory follicles → the presence of FF IL-12 has been associated with fertilization failure

Tumor necrosis factor α

- regulating ovarian function, exerting an influence on proliferation, differentiation, follicular maturation, steroidogenesis and apoptosis
- TNFa is expressed by the oocyte, theca cells, GCs and corpora lutea
- increased levels of FF TNFa in women with PCOS are significantly and inversely correlated to FF E2 levels, which is again indicative of poor-quality oocytes and embryos

Soluble Fas and sFas ligand

- sFas and sFasL proteins exert anti- and pro-apoptotic functions
- The binding of sFasL with its receptor induces apoptosis, whereas sFas, acting as a functional antagonist, binds with sFasL to inhibit sFasL-mediated apoptosis by preventing death signal transduction
- sFas levels in the FF are positively correlated to oocyte maturity and survival in IVF patients
- Patients with PCOS who are treated with metformin display antiapoptotic effects owing to elevated serum sFas levels and reduced FF sFasL levels

(Other microenvironment factors)
Homocysteine

- Many studies have established that elevated Hcy levels in serum and FF are inversely associated with oocyte and embryo quality, resulting in decreased fertilization and pregnancy rates, and increased miscarriage rates in PCOS patients undergoing IVF treatment
- elevated levels of Hcy in FF and serum may suppress E2 synthesis → interfere with ovarian follicular developmental competence, oocyte maturation and fertilization in women with PCOS

Leptin

- as a biomarker for body fat
- to predict oocyte maturity and embryo quality
- High leptin levels → decreased oocyte maturity, poor fertilization and embryo quality, and lower pregnancy rates in PCOS patients
- Others suggest that elevated leptin levels in the ovary may block E2 production, disturbing follicular development and oocyte maturation
- Hyperleptinemia, or increased FF leptin, in PCOS patients may impair embryo quality and pregnancy rates

FF meiosis-activating sterol

- FF meiosis-activating sterol (FF-MAS) is an endogenous signaling molecule and an intermediate in the cholesterol biosynthetic pathway
- Many IVM studies : exposure to FF-MAS can promote nuclear and cytoplasmic maturation of the oocyte and improved fertilization and early embryonic development in humans and other mammals

Immunoreactive corticotrophin-releasing hormone, tissue inhibitor of metalloproteinase-1 & 2 and visfatin

- Immunoreactive corticotrophin-releasing hormone (IrCRH) is synthesized by theca cells and/or the mature oocyte itself
- Study: decreased FF IrCRH levels are correlated with oocyte dysfunction in women with PCOS
- In a recent study, serum visfatin levels were significantly increased in women with PCOS

Renin

- ovarian renin has an impact on the developmental and fertilization competence of human oocytes
- decreased FF renin is related to increased rates of oocyte maturation and fertilization, and better subsequent embryo quality

Resistin

- there are no significant differences in either serum or FF resistin concentrations between PCOS patients and controls
- these are also not significantly correlated with fertilization rates, implantation rates, clinical pregnancy rates or early miscarriage rates in PCOS patients

Oxidative stress

- Reactive oxygen species (ROS) are involved in many physiological functions and act as mediators in a variety of signaling pathways.
- PCOS: increased FF ROS and decreased total antioxidant capacity and superoxide dismutase are closely associated with lower rates of oocyte maturation and fertilization, poor embryo quality and decreased pregnancy rates

- ROS degrade polyunsaturated lipids, forming malondialdehyde (MDA)→ Elevated FF MDA levels are directly correlated with increased numbers of immature oocytes retrieved, lower rates of fertilization and embryonic development, lower pregnancy rates in PCOS patients

Concluding remarks

- Patients with PCOS are typically characterized by production of an increased numbers of oocytes during stimulation in an IVF cycle
- however, these women suffer from poor-quality oocytes and embryos, lower fertilization, cleavage and implantation rates, and higher miscarriage rates

- A series of extra- and intra-ovarian factors causing abnormalities during folliculogeneis, follicular growth and oocyte meiotic maturation processes have been identified.
- Whether these abnormalities have a direct influence on GC–oocyte interactions and oocyte meiotic maturation, fertilization, embryonic development and pregnancy, or whether the influences are through circulating endocrine and local paracrine/autocrine mechanisms, requires further clarification.

Thanks for your attention !