Το σύνδρομο των πολυκυστικών ωοθηκών και υπογονιμότητα κατά την διάρκεια της ζωής της γυναίκας

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ΑΛΕΞΑΝΔΡΟΥΠΟΛΗ 2020
Polycystic Ovarian Syndrome and Infertility in a woman's lifetime

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ALEXANDROUPOLI 2020
Acknowledgments

I would like to thank my supervisor Prof D.G. Goulis for assisting me in the completion of this thesis under time restraining circumstances. I would also like to express my gratitude to Prof N. Nikolettos who is the cornerstone of this esteem postgraduate study programme and Prof V. Asimakopoulos who have both generously devoted their time and shared their deep knowledge and expertise. Furthermore I would like to acknowledge Prof E. Papanikolaou for the support and encouragement required for completing any task one aspires to achieve and of course I could not refrain from mentioning S. Kiriaki. If Prof Nikolettos is the mind of this programme she is the soul, thank you for being so supportive, considerate and thoughtful. But above all I would not be able to achieve anything without all the love and support of my family, my husband, our lovely daughter and our two mischievous, young boys, love you to bits.
ΠΕΡΙΛΗΨΗ
Το Σύνδρομο των Πολυκυστικών Ωυθηκών είναι η συνηθέστερη ενδοκρινολογική πάθηση στις γυναίκες και ο κυρίαρχος αιτιολογικός παράγοντας ανωθυλακιορρηκτικής υπογονιμότητας. Η παθοφυσιολογία της ΣΠΩ είναι πολύπλοκη και πολυπαραγοντική, χωρίς να είναι ακόμα πλήρως κατανόητη. Οι τρεις χαρακτηριστικές ενδοκρινολογικές διαταραχές που παρατηρούνται, η υπερέκκριση της LH, ο ωοθηκικός υπερανδρογονισμός και η αντίσταση στην ινσουλίνη, δρουν συνεργαία, υπερανδρογονισμός και αναπαραγωγικό, και συνεισχένται σε ένα φάσμα αναπαραγωγικών, και ενδοκρινολογικών φαινοτύπων, τα μπορεί να εκδηλωθούν πρώιμα από την περίοδο της εφηβείας και να εκτυλιχθούν κατά τη διάρκεια της ζωής της γυναίκας. Τα κριτήρια Rotterdam υποστηρίζονται από τις πρόσφατες κατευθυντήριες οδηγίες της Αμερικανικής και Ευρωπαϊκής εταιρίας αναπαραγωγής. Η μέτρηση των επιπέδων της AMH στο πλάσμα αίματος θα μπορούσε να αποτελέσει ένα διαγνωστικό εργαλείο μελλοντικά, εφόσον τυποποιηθούν οι μέθοδοι μέτρησης και οι τιμές κατοφλιού. Περαιτέρω κατανόηση της διαταραχής της ωοθυλακιογένεσης θα μπορούσε να βοηθήσει στην εφαρμογή στοχευμένων θεραπειών, αποκαθιστώντας όχι μόνο την ωοθυλακιορρήξια αλλά και την αναπτυξιακή επάρκεια των ωρίων, βελτιώνοντας τα αναπαραγωγικά αποτελέσματα των τεχνικών εξωσωματικής γονιμοποίησης. Συστήνεται η εξατομικευμένη και διεπιστημονική θεραπευτική προσέγγιση που συμπεριλαμβάνει πρωταρχικά τροποποίηση του τρόπου ζωής και δευτερεύοντος φαρμακευτικές παρεμβάσεις. Ο στόχος κάθε θεραπευτικής προσέγγισης είναι ολιστικός και στοχευμένος στην επαναφορά της ωοθυλακιορρήξιας αλλά και την αποφυγή μελλοντικής σχετικής με το σύνδρομο νοσηρότητας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ
ΣΠΩ, ανωθυλακιορρηκτική υπογονιμότητα, υπερανδρογονισμός, αναπτυξιακή επάρκεια ωρίων
ABSTRACT
PCOS is the commonest endocrine abnormality in women, and the leading etiology of anovulatory infertility. Its pathogenesis is complex, multifactorial, and not yet fully understood. Its three cardinal features of LH hypersecretion, ovarian hyperandrogenism, and insulin resistance interlink leading to a spectrum of reproductive, metabolic and endocrine abnormalities presenting as early as puberty and evolve throughout a woman’s lifetime. The Rotterdam criteria are endorsed by the most recent guideline committees. AMH serum levels could be used in the future as PCOS screening tool once methods and cut off values standardized. Further understanding of the disruption in folliculogenesis could help implement targeted treatments, restoring oocyte developmental competence improving IVF reproductive outcomes. An individualized, multidisciplinary therapeutic approach is recommended implementing lifestyle and pharmacologic interventions so as to overcome unovulatory infertility and future associated co-morbidities.

KEYWORDS
PCOS, unovulatory infertility, hyperandrogenaemia, oocyte competence
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Introduction

The subject of this dissertation is Polycystic Ovarian Syndrome (PCOS) and the issues that may arise where a woman’s fertility is concerned during her reproductive years. PCOS is the most frequent endocrine disturbance that women may come up against during their lifetime, affecting 9–18% of the general population (March et al., 2010; Yildiz et al., 2012). It is a multifactorial condition that carries a genetic predisposition of still not well-established etiology. Its symptomatology mainly features menstrual cycle disturbances and hyperandrogenism affecting women differently in different parts of their life. As examples, a young adolescent girl could present with low self-esteem and depression due to acne and hirsutism, another seeking advice on oral hormonal contraception due to irregular cycles and oligomenorrhea. In contrast, others could face difficulty conceiving or require further management due to increased risk of endometrial hyperplasia, obesity, type 2 diabetes, and cardiovascular disease. The scope of this essay is to lay out the current knowledge on the diagnostic criteria, etiology, and presentation of PCOS while focusing on its effect on fertility and exploring available management options, which will enable these couples to embrace the gift of parenthood while leading a healthier lifestyle.
Main body of dissertation

1a. Background

PCOS is a hormonal disorder commonly encountered by women throughout their reproductive life. Its prevalence ranges from 5% to 15% depending on the population and diagnostic criteria applied (Dumont et al., 2015; Azziz et al., 2004; Zawadski and Dunaif, 1992; Franks et al., 1995; Rachow et al., 2012) and accounts for about 80% of anovulatory infertility cases (Balen et al., 2016). The very first published case of the syndrome was in 1721 in Italy (Kovacs et al., 2007) but the first description of the Syndrome was by Irving F Stein and Michael L. Leventhal in 1935 leading to the syndrome sometimes being referred to as Stein and Leventhal Syndrome. Nowadays, with the improved understanding of the syndrome and the wider implications it might entail, not only reproductive but also metabolic and psychological, the term PCOS can be misleading.

1b. Clinical presentation

PCOS exhibits a heterogeneous presentation with ethnic variation (Wijeyeratne and Balen., 2013), covering a broad clinical spectrum ranging from mild phenotypes of eumenorrheic women with polycystic ovarian morphology and sporadic anovulation to more severe cases of both reproductive, endocrinologic and metabolic disturbances. A detailed personal history and a meticulous physical exam are both necessary for the early and impromptu recognition of the syndrome.

Women can complain of irregular, infrequent, or absent menstruation for long periods. These disturbances can start during puberty, around the time of menarche, or later on (Mayo clinic). They usually subside after the age of 40 (Kourtis and Makedou., 2015).

According to the recent 2018 ASRM recommendations, a menstrual cycle is defined as irregular:

• if 1 to less than three years post-menarche its duration is less than 21d or more than 45
• if more than three years post-menarche to perimenopause the cycle length is less than 21d or more than 35 or less than eight cycles in a year

• if 1 year post-menarche there is secondary amenorrhea for more than 90d for any one cycle

• if primary amenorrhea by the age of 15 years or at any age more than three years post-thelarche. In any of the above cases, the presence of PCOS should be considered and further investigated.

The second characteristic feature of PCOS is hyperandrogenism (HA). HA can either be clinical with hirsutism, male pattern baldness, acne, and oily skin or biochemical with elevated androgen serum levels. Hirsutism is defined by excess terminal hair growth in androgen-dependent sites and is distinctive to hypertrichosis, excessive hair growth that affects any part of the body in both genders. Terminal hairs clinically grow >5 mm in length if untreated, varying in shape and texture and generally being pigmented. The amount and location of hair growth are measured by the Ferriman-Gallwey score, published in 1961 by D. Ferriman and J.D. Gallwey in the Journal of Clinical Endocrinology.

**Figure 1.** Graphic representation of Ferriman-Gallwey score, Source: NEJM.

In the original score, 11 areas were included, but in the modified version, only nine are evaluated, the forearm and shin areas are excluded as hair growth in these areas is non-
androgen sensitive but somewhat familial and racial. Each area is assigned a score from 0 (no terminal hair) to 4 (excess hair growth), and the sum of all individual scores provides a total hirsutism score. A total score of more than 8 signifies hyperandrogenism. The severity of hyperandrogenism is proportional to the score. It is essential to mention that the score is affected by the patient’s ethnic background as a lower than 8 score is considered normal for Asian populations while a higher than 8 for Mediterranean women. (Kourtis and Makedou., 2015).

As about alopecia, the Ludwig visual score is preferred for assessing the degree and distribution of female alopecia (Figure 2) (Teede et al., 2018). It was developed in 1977, classifies female pattern baldness into three grades ranging from perceptible crown thinning to total denudation of the area. It is the most widely used system despite not incorporating the accentuation of fronto-vertical alopecia and male pattern hair loss. So far, there is no evaluation scoring system for acne that is universally established.

![Figure 2. Ludwik’s classification of female hair loss](image)

When the external signs of HA are absent or unclear, assessment of biochemical HA is necessary for establishing PCOS diagnosis. According to the recent ASRM recommendations of 2018, free testosterone, free androgen index, or calculated high-quality assays preferably measure bioavailable testosterone. Techniques such as liquid chromatography-mass spectrometry (LCMS) and extraction chromatography immunoassays should be used for the most accurate assessment of total or free testosterone. Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in the assessment of biochemical hyperandrogenism in PCOS, as they demonstrate reduced sensitivity, accuracy, and precision. Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be
considered if total or free testosterone are not elevated, providing, however, limited additional information in the diagnosis of PCOS. Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. When assessing biochemical HA in women on oral hormonal contraception, a three month or more period of withdrawal is recommended before reliable measurement, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production.

Lastly, as the syndrome's name suggests, a polycystic appearance of the ovaries can be seen in transvaginal ultrasonography. The ovaries are enlarged, with mostly small, peripherally located follicles, resembling a "string of pearls". The ovarian stroma is hyperechoic, and the outline of the ovary irregular.

![Figure 3. Anatomical and sonographic appearance of normal compared to polycystic morphologically ovaries](image)

For an ovary to be characterized as polycystic morphologically, the sonographic evaluation should ideally be performed transvaginally, during the early follicular phase and 12 or more follicles measuring 2 - 9 mm in diameter or an ovarian volume >10 ml (length x width x depth x 1/2) of any of the two ovaries should be measured according to the 2004 Rotterdam criteria. We need to bear in mind that this finding alone is not specific to PCOS, and it can be found in up to 22% of healthy women of the general population (Kourtis and Makedou, 2015) and 68% of 19 - 21-year-old as a Danish study demonstrated by Kristensen et al., 2010. Due to advances in ultrasound technology and modern-day high-resolution ultrasound alongside high AFC in younger women, Androgen Excess and PCOS Society has reviewed current data and published
updated guidelines for PCOM diagnosis, increasing the antral follicle count to 25 per ovary, in order to avoid overdiagnosis

1c. Diagnostic criteria

PCOS exhibits a great phenotypic variability requiring a common consensus where it comes to setting the diagnosis. After the first description by Stein and Leventhal (1935), the diagnostic criteria of PCOS have been developed, challenged, changed, and evolved over the years. The 1990 National Institute of Health (NIH) conference proposed the diagnostic criteria of oligo- or anovulation and biochemical and clinical signs of hyperandrogenism (HA). The 2003 Rotterdam consensus workshop of the ASRM and the European Society of Human Reproduction and Embryology (ESHRE) broadened the definition by including polycystic ovary (PCO) morphology and requiring 2 out of 3 criteria for the diagnosis (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The newly added PCOS phenotypes were PCO with irregular menstruation (IM) without hyperandrogenism (HA) and PCO with HA without oligo-anovulation. Therefore, PCOS can be divided into four subtypes: (i) IM/PCO/HA, (ii) IM/PCO, (iii) IM/HA (iv) HA/PCO. In 2006, the Androgen Excess Society (AES) Task Force on the Phenotypes of PCOS emphasized androgen excess as the cornerstone of PCOS accompanied by oligomenorrhoea or polycystic ovarian morphology or both (Azziz et al., 2006), excluding women with irregular periods, PCOM without HA (type ii subtype). According to the latest ESHRE and ASRM recommendations for the assessment and management of polycystic ovarian syndrome 2018, the Rotterdam diagnostic criteria are endorsed for the diagnosis of the syndrome in the adult population.

PCOS can present during adolescence. Its presenting signs, however, can be overlapping with physiological changes that generally occur in puberty complicating the diagnosis process (Roe and Dokras., 2011). During the early years after menarche, most cycles are anovulatory (in the first two years of menarche half of the menstrual cycles are anovulatory) due to the hypothalamic-pituitary-ovarian axis immaturity, multiple follicles on ultrasound are common, and acne is widely bothersome and other hyperandrogenism evidence challenging to interpret. The benefits of early syndrome diagnosis, however, are undeniable as it could lead to earlier treatment and reduction in long term PCO-related morbidity but should be sought with caution due to the psychological burden or unnecessary treatment of early diagnosis (Agapova et al., 2014). A way out of this conundrum was attempted by Carmina et al. 2010, and the 2012
ESHRE/ASRM criteria Workshop Group that define PCOS for adolescents by the presence of all three of the Rotterdam 2003 criteria (polycystic ovarian morphology, hyperandrogenism, and chronic anovulation) while Sultan and Paris, 2006 proposed requiring four out of five of clinical hyperandrogenism, oligomenorrhea or amenorrhea at least two years post menarche, biologic hyperandrogenism, insulin resistance, and polycystic ovary morphology (Carmina et al., 2010; Sultan and Paris, 2006; Fauser et al., 2012). In the recent ASRM updated guidelines of 2018, oligo-anovulation and hyperandrogenism are required, while pelvic Ultrasound is not recommended for the diagnosis. In cases where the presenting phenotype is not sufficient to meet diagnostic criteria, the adolescent is best considered as high risk and could be reassessed at or before full reproductive maturity (8 yrs post menarche) (Teede et al., 2018). Deferred diagnosis attempts to avoid overdiagnosis with its potential for premature labelling, anxiety, and unnecessary interventions.

PCOS diagnosis remains mostly a diagnosis of elimination as all other causes of hyperandrogenism and menstrual irregularities need to be excluded first. In the differential diagnosis, one needs to consider thyroid gland dysfunction, hyperprolactinemia, non-classical congenital adrenal hyperplasia, virilizing ovarian, and adrenal tumors, Cushing’s syndrome, drug-induced androgen excess (Spritzer, 2014).

Recent studies have shown evidence that measuring anti-Müllerian Hormone (AMH) can be an objective serum marker for the diagnosis of PCOS, overcoming the variability in the sonographic polycystic ovarian morphology assessment due to device advances, examiners’ experience and practical difficulties due to high BMI or puberty (Rasquin and Mayrin, 2019).

AMH is a member of the Transforming Growth Factor-β (TGf-β) superfamily. It was first isolated and purified in 1984 (Rajpert-De Meyts et al., 1999). AMH acts as an intrafollicular growth modulator. It is produced by the granulosa cells of non-FSH depended antral (2 - 9mm) and pre-antral (<2mm) follicles (Sahmay et al., 2014). AMH acts as a gatekeeper of follicular growth, as it rises, it inhibits further recruitment of primordial to primary follicles from the follicular pool. At the same time, it regulates FSH effect on the aromatase activity. The rising levels of estrogens confine AMH's action through an intrafollicular negative feedback loop, which ensures that each small antral follicle produces little E2 before the selection of the dominant follicle takes place, but at the same time restricting AMH secretion to follicles up to 8 mm in diameter. These follicles ranging from 2-8mm are the ones being measured on
Ultrasound ovarian evaluation accounting for the so-called antral follicle count (Jeppesen et al., 2013). So AMH could be a hormonal marker of the antral follicle count and indirect expression of the ovarian reserve (Rosenfield et al., 2012). AMH is independent of the Hypothalamus-pituitary axis and the action of FSH (Tran et al., 2011), it has minimal inter and intra-cycle variability (Fanchin et al., 2005; Hehenkamp et al., 2006) and it also gives a more profound vision of the growing follicular pool as it is also expressed by pre-antral follicles, that is hardly ever seen on ultrasound. AMH levels are higher in PCOS patients. They are noted to be higher in cases with hyperandrogenism and insulin resistance (Fleming et al., 2005), thus reflecting the severity of the syndrome and the degree of folliculogenesis disruption. In a study by Sahmay et al., 2014 a combination of AMH (cut off value of 3.8 ng/ml) combined with androgenic and oligo/amenorrhea status showed an 83% sensitivity and 100% specificity for patients previously diagnosed with PCOS according to the Rotterdam Criteria. However, despite aspirations for AMH to emerge as a biochemical marker and diagnostic tool for PCOS, it still lacks standardization of assays and established cut off thresholds based on large scale validation studies across a wide range of ages and ethnicities. Thus so far AMH should not be used as a single discriminatory test for the diagnosis of PCOS, yet (Teede et al., 2018) and the value of pelvic ultrasound in the monitoring of response in ovulation induction and the ovarian morphology, endometrial thickness and uterine anatomy as a whole is irreplaceable (Balen et al., 2016).
2. Pathophysiology

The pathogenesis of PCOS is complex, multifactorial, and not yet fully understood. There are three cardinal features present; LH hypersecretion, ovarian hyperandrogenism, and insulin resistance that interconnect, resulting in disrupted reproductive and endocrine function. According to the two-cell, two gonadotropin hypothesis, LH acts on the theca cells of recruited follicles to synthesize androgens utilizing circulating cholesterol while FSH enhances aromatase activity of granulosa cells, converting androgens to estrogens (Liu and Hsueh, 1986). Rising levels of estrogens promote granulosa cell proliferation, FSH, and LH receptor expression and, along with inhibin B down-regulate further FSH/LH secretion from the pituitary, ensuring monofollicular dominance. Once, however, a critical concentration of circulating estrogens is reached, a positive feedback estrogen-mediated loop is activated, resulting in an LH surge and the cascade of events that lead to ovulation. It seems that the key to successful follicular development largely depends on the follicle's ability to convert its initial androgenic to an estrogenic environment.

In PCOS, there seems to be inherent ovarian hyperandrogenism. This increased androgen biosynthesis is sustained by an elevated pulsatile LH secretion and aggravated by the presence of hyperinsulinemia due to insulin resistance. The developing hyperandrogenemia induces further LH secretion while circulating estrogens inhibit pituitary FSH resulting in abnormal folliculogenesis, failure of dominance, and follicular arrest. Obesity is an acquired compounding factor by increasing insulin resistance and further suppressing FSH by adipose tissue androgen conversion to estrone.

In 1994, Poretsky and Piper, after reviewing available literature, proposed the dual defect hypothesis. They postulated that two independent genetic defects that of LH excess and insulin resistance work synergistically to cause the presenting and biochemical features of PCOS.

Abbott et al., 2002, published the Developmental hypothesis in an attempt to explain the heterogeneous phenotype associated with the syndrome with a unifying linear model. Abbott and his team postulate that there is a genetically predetermined ovarian hypersecretion of androgens at puberty or possibly even in utero, which ‘programs’ the hypothalamus and pituitary to favor increased LH secretion possibly by diminishing steroid negative feedback
resulting in abnormal LH secretion and predisposition to central adiposity, which worsens insulin resistance (genetic or environmentally imposed i.e. by obesity).

On the same lines of a strong genetic predisposition, recently the "2-hits" hypothesis has been suggested (Rosenfield and Ehrmann., 2016) in order to explain how the different abnormalities interconnect. It proposes that PCOS is the result of a congenitally programmed predisposition (first hit-congenital ovarian dysfunction, congenital virilization, disturbed fetal nutrition), which is expressed due to a provocative environmental factor (second hit-insulin resistance hyperinsulinemia, exaggerated adrenarche, obesity).

The intricate and complex pathophysiology is outlined in the diagram depicted below.

**Figure 4. Pathophysiology of PCOS**
3. Complications

PCOS’s accurate and prompt diagnosis is essential, as fore mentioned, due to potential short and long-term effects on a woman’s wellbeing and longevity.

For a young woman, in her reproductive years, wishing to have a family, having PCOS could have a detrimental effect on her fertility and reproductive capacity. Infertility was one of the main symptoms attributed to PCOS when it was first described in 1935 (Stein, Leventhal). Subsequent epidemiologic data showed that 70% have fertility issues compared to healthy women. In a large population study of 1,741 women diagnosed with PCOS, 50% experienced primary infertility, and 25% reported secondary infertility (Balen et al., 1995). PCOS accounts for 80% of anovulation cases. Time to achieve pregnancy is long, but the reproductive outcome is similar to that of non-PCOS women (Koivunen et al.,2008; Hudecova et al., 2009). The typical PCOM appears to diminish with advancing age (Korhonen et al., 2003), and menstrual cycles normalize (Elting et al., 2000). This waning of symptoms could be attributed to the fall of inhibin B produced by the diminishing number of follicles, which is essential and permissive of thecal androgen production (Winters et al., 2000). PCOS women with anovulatory infertility appear to have a better ovarian reserve and seem to have a longer reproductive window with advancing age compared to infertile ovulatory women (Kalra et al., 2013; Mellembakken et al., 2011). Live birth rates and miscarriage rates are similar between PCOS and healthy controls, and in more than 2/3 of pregnancies occurred spontaneously (Hudecova et al., 2009). According to the guidelines of the Endocrine Society-appointed Task Force of experts (Legro et al., 2013) PCOS is a risk factor of infertility only in the presence of oligo-anovulation, while to Teede et al., 2018, ovulation dysfunction can still occur with regular cycles, so besides using menstrual history as a screening tool, anovulation can be confirmed using mid-luteal serum progesterone concentration.

During IVF for patients with anovulatory PCOS more oocytes are retrieved but appear to be more immature and of poor quality leading to lower fertilization, cleavage, blastulation, implantation and higher miscarriage rates (Sengoku et al., 1997; Ludwig et al.; Mulders et al.,2003; Sahu et al., 2008; Boomsma et al., 2008). Initially, this observation was attributed to higher aneuploidy status (Munne et al., 1995; Gianaroli et al., 2003,2007). Subsequent data, however, suggested that women with PCOS have a higher number of oocytes and produce more euploid embryos but still result in lower pregnancy and higher miscarriage rates after
high oocyte yields, which are not genetically associated (Weghofer et al., 2007). Therefore, other factors apart from chromosomal are likely to be involved in the increased risk of pregnancy loss in PCOS patients (Sagle et al., 1988; Wood et al., 2007; Weghofer et al., 2007).

These analyses demonstrated that normal and PCOS oocytes that are morphologically indistinguishable and of high-quality exhibit different gene expression profiles (androgen and other nuclear receptor activators) suggesting that defects in meiosis or early embryonic development may contribute to reduced developmental competence of PCOS oocytes (Wood et al., 2007). Impaired oocyte and embryonic developmental competence in PCOS could be associated with abnormal endocrine/paracrine factors, metabolic dysfunction and alterations of the intrafollicular environment that disturb normal cumulus cell-oocyte signalling during folliculogenesis and follicle maturation (Franks et al., 2002; Dumesic and Abbott, 2008, Wood et al., 2007). Poor meiotic spindle visualization and higher ROS (reactive oxygen species) levels in women with PCOS could indicate a poorer oocyte and embryo quality due to an impaired antioxidant defence mechanism in the follicular fluid (Rajani et al., 2012). Alterations of oocyte competence could be a potential aetiological factor for subfertility in PCOS; its contribution to reproductive potential is variable and dependent on the PCOS phenotype and associated co-morbidities (Palomba et al., 2017). Complex endocrine disorders such as LH hypersecretion, FSH deficiency, hyperandrogenemia and hyperinsulinemia responsible for the pathogenesis of PCOS, could impair the oocyte-cumulus dialogue, alter the follicular micro-environment, leading to suboptimal oocyte developmental competence and subsequently hinder implantation success (Van Der Spuy and Dyer, 2004; Dumesic and Abbott, 2008; Boomsa et al., 2008; Franks et al., 2008).

**Oocyte competence-quality**

First of all, oocyte developmental competence encompasses the intrinsic oocyte dynamic to undergo meiotic maturation, fertilization, proper embryonic development, and achieve pregnancy (Decanter, 2018). It requires the synchronous maturation of both the nucleus and the cytoplasm via mechanisms that are poorly understood. The morphological modifications the oocyte undergoes as it develops facilitate its increasing energy and nucleic acid requirements that need to be met in order to achieve meiotic and embryological development competence.
**LH hypersecretion**

Women with PCOS show increased LH pulse frequency and amplitude during the follicular phase of their menstrual cycles (Balen et al., 1993; Cano et al., 1997 a,b; Van Der Spuy and Dyer, 2004). Sustained elevated LH levels have been associated with impaired oocyte maturation, fertilization, and embryo quality. This, in turn, translates into lower pregnancy rates and raised miscarriage rates (Adams et al., 1985; Ludwik et al., 1999; Van der Spuy and Dyer, 2004; Santos et al., 2010). Increased LH pulsatile secretion may suppress FSH function, resulting in abnormal granulosa cell function, premature luteinization, the follicular arrest of small antral follicles, and premature oocyte maturation (Van Der Spuy and Dyer, 2004; Dumesic et al., 2007b; Franks et al., 2008). LH could lead to cell apoptosis by damaging the oocytes nucleus activating a cascade of premature meiotic processes, possibly via a receptor-coupled signal transduction system (Yoshimura and Wallach, 1987; Kurzawa et al., 2008). Disruption of the meiotic control mechanism orchestrating normal chromatid segregation and first polar body extraction could jeopardize oocytes' chromosomal integrity (Sengoku et al., 1997), contributing to embryonic aneuploidy. This premature exposure to elevated LH levels may explain the increased miscarriage rates in women with PCOS (Balen et al., 1993; Urman et al., 2004). However, increased numbers of oocytes available for insemination or ICSI compensate for decreased fertilization rates and embryo quality (Urman et al., 2004). However, other studies postulated that women with PCOS are not at increased risk for embryonic aneuploidy in the course of in vitro fertilization treatment and that lower pregnancy rates after high oocyte yields are not due to a genetic cause requiring further investigation (Weghofer et al., 2007).

**FSH deficiency**

FSH is responsible for the recruitment of immature follicles 2-5mm and follicular growth. It acts on the granulosa cells of 6-8mm follicles and helps them acquire aromatase activity initiating the gradual increase in estrogen production by utilizing the theca cell androgen substrate (Leu XY, Hsueh AJ, 1986; Dumesic and Abbott, 2008). In the late follicular phase, pituitary FSH secretion declines due to the negative feedback loop mediated by the inhibitory effects of rising concentrations of oestradiol and inhibin B. This ensures a single dominance of the most advanced metabolically follicle and its further maturation and ovulation. In the late luteal phase, subordinate follicles undergo atresia except for the few that are rescued by the
slight increase in FSH, important in the initiation of the next ovulatory cycle (Erickson and Shimasaki, 2001; Padhy et al., 2009). In PCOS, FSH serum levels are lower than normal (Hillier, 1994). This FSH deficiency leads to antral follicle accumulation (Franks et al., 2008). The high number of smaller follicles indicates that many have undergone premature arrest and failed to become dominant follicles (Franks et al., 2008) but maintain their steroidogenesis function. However, the developmental competence of oocytes collected from women with PCOS can be normal, leading to similar fertilization and cumulative pregnancy rates as non-PCOS women with optimizes ovulation induction (Hardy et al., 1995; Ludwig et al., 1999). The increased number of oocytes retrieved compensate for the lower fertilisation rates resulting in similar pregnancy and live birth rates (Heijnen et al., 2006).

In the IVF setting, PCOS women undergoing stimulation exhibit elevated E2 concentrations, significantly higher number of oocytes retrieved, less high-quality oocytes, reduced fertilization rates, increased embryonic fragmentation, decreased blastulation, and implantation rates (Cano et al., 1997a;b; Urman et al., 2004). Presumably, high E2 serum concentrations are associated with a deleterious effect on oocyte maturation and embryonic development (Hardy et al., 1995).

**Hyperandrogenaemia**

Elevated LH increases androgen production and secretion by ovarian theca cells. However, LH excess is probably the result rather than the cause of hyperandrogenaemia. Possible escape desensitization enables theca cells to become more sensitive to LH, which aggravates ovarian HA (Rosenfield and Ehrmann, 2016). Androgen excess is mainly of ovarian origin with a significant contribution from the adrenals and, to a lesser extent, from peripheral adipose tissue (Van der Spuy and Dyer, 2004; Nisenblat and Norman, 2009). It has been hypothesized that there is an intrinsic theca cell steroidogenic dysregulation (Rosenfield and Ehrmann, 2016). Increased androgen concentrations in the follicular fluid are associated with increased plasma levels, antagonize estrogen effects, enhance granulosa cell apoptosis and may block dominant follicle development, cause follicular arrest and degeneration, (Billing et al.,1993; Kurzawa et al., 2008). It has been hypothesized that HA may have a negative effect on oocyte competence (Brzynski et al., 1995; Jabara and Coutifaris, 2003). Results from in-vitro models on cumulus cell-free and cumulus cell enclosed mouse oocytes demonstrate that testosterone exerts an inhibitory effect on meiotic maturation on the CC-free oocytes demonstrating a protective
function of cumulus cells via local aromatase activity in both human (Dumesic et al., 2007b) and mice (Andreriesz and Trounson, 1995). CC function’s crucial role in folliculogenesis is seen in small PCOS follicles that are hyperandrogenic (Eden et al., 1990; Dumesic, 2007b) due to intrinsically increased androgen synthesis by theca cells (Nelson et al., 2001). Data from a murine PCOS model induced by DHEA showed that DHEA treated mice produced fewer MII oocytes, with normal spindle assembly but decreased mtDNA copy number, ATP content, inner mitochondrial membrane potential, and excessive oxidative stress, suggesting that a mitochondrial dysfunction impairs cytoplasmic oocyte maturation compromising oocyte competence (Huang et al., 2015). Further evidence suggests that androgens decrease intrafollicular calcium oscillations inhibiting cytoplasmic maturation, effecting meiotic maturation (Tesaric and Mendosa 1995, 1997; Jabara and Coutifaris, 2003). Furthermore, high androgen levels are associated with higher miscarriage rates (Van der Spuy and Dyer, 2004), suggesting that HA may have a detrimental effect on folliculogenesis and endometrial cell growth and secretory activity (Okon et al., 1998; Tuckerman et al., 2000).

Hyperinsulinaemia

A major extra-ovarian factor in the steroidogenic dysregulation and Diabetes mellitus related comorbidities of PCOS is insulin resistant hyperinsulinism (Rosenfield et al., 2001; Diamanti-Kandarakis and Dunaif, 2012). Hyperinsulinemia augments LH stimulation of ovarian androgen production, which results in oocytes lower quality, post maturity (Cano et al., 1997a, b). Data from in vitro cell-culture models suggest that insulin promotes FSH mediated Granulosa cell LH receptor up-regulation, inhibiting FSH dependant aromatase activity, thus reducing fertilization and blastulation rates (Dumesic et al., 2002; Dumesic et al., 2007; Eppig et al.,1998). High insulin levels may impair oocyte developmental competence leading to reduced fertilization, embryonic development, and implantation in PCOS obese women (Cano et al., 1997b; Jabara and Coutifaris, 2003; Dumesic and Abbott, 2008; Boomsma et al.,2008). Insulin has been shown to act upon PCOS theca and normal granulosa cells, stimulating follicular recruitment (Dumesic et al., 2002, Kezele et at, 2002), changing multiple gene expression altering meiotic and mitotic spindle dynamics and centrosome function in PCOS oocytes (Wood et al., 2007). This indicates that insulin may be an essential mediator of oocyte developmental competence via a ligand-receptor regulating system (Dumesic et al., 2007b).
Additionally, PCOS carries an increased prevalence of cardiovascular disease, obesity, hypertension, dyslipidemia, obstructive sleep apnea, impaired glucose tolerance, and diabetes mellitus (DM). DM’s prevalence, in PCOS patients, is a 5-fold, 4-fold, and 3-fold increase in Asia, America, and Europe, respectively, independently, though exacerbated by obesity. It is also associated with a higher risk of obstetric complications such as gestational diabetes and pregnancy-induced hypertension and pre-eclampsia (Palomba et al., 2014). Specifically, the risk of pregnancy-induced hypertension and preeclampsia was 12.7% and 8%, respectively, and significantly higher than those observed in healthy controls (5.3% and 2%).

Recent meta-analyses have shown that women with PCOS, of all ages, are predisposed to endometrial hyperplasia and endometrial cancer (Barry et al., 2014). According to Tedee et al., there is a 2 - 6-fold increased risk for endometrial carcinoma, especially in the perimenopause period. The long-standing effect of anovulation with the unopposed estrogentic action on the endometrium and hyperandrogenism is a potential pathophysiologic mechanism without, however, being able to exclude the possible contributing or aetiologic effect of hyperinsulinemia, hyperglycemia, inflammation, and obesity (Giovannucci et al., 2007). As far as breast and ovarian cancer are concerned due to limited and contradictory evidence regarding the associated risk in PCOS, no routine surveillance strategy is recommended by the ASRM/ESHRE consensus statement (Fauser et al., 2012).

The psychological impact of this life-long disease, associated with so many co-morbidities and body image challenges, due to commonly encountered obesity and hyperandrogenism symptoms, is substantial. Depression prevalence rates range from 14 - 67%, with a 4-fold increased risk of depressive symptoms, compared to age-matched women (Hudecova et al., 2009). The women's quality of life is further affected by an increased risk of anxiety disorders, body image disorder, eating disorders, and psychosexual dysfunction, to the extent that psychological screening should be routinely performed (Tedee et al., 2018) for early recognition and therapeutic action.
4. Therapeutic approaches

Timely and individualized care is essential in preventing associated comorbidities and improve the quality of life of women with PCOS. As the syndrome exhibits high heterogeneity, so makes the therapeutic approach reflecting each time the aspect that needs to be attended to each time while bearing in mind the long-term consequences. The main framework of the therapeutic approach when it comes to PCOS related anovulation are lifestyle changes, ovulation induction, and as a last resort IVF therapy (Balen et al., 2016), as depicted in Figure 5.

**Figure 5.** ESHRE consensus algorithm for the treatment of anovulatory PCOS.

4a. Lifestyle changes

Lifestyle interventions are recommended to be implemented for 3 - 6 months before any pharmacological therapy. The aim is to improve the metabolic and endocrine profile of the patient in order to restore menstrual cyclicity and ovulation while reducing obstetrical risks and improving the long-term quality of life of the patient and her offspring. The three cornerstones of lifestyle modifications in PCOS are optimizing body weight, diet, and exercise
while offering the necessary psychosocial support to ensure compliance.

Many studies have shown that women with PCOS have a higher prevalence of weight gain and obesity (Glueck et al., 2005; Teede et al., 2013). Excess weight exacerbates hyperandrogenism and hyperinsulinemia, increasing the risk of developing PCOS and aggravating its metabolic, reproductive, obstetric, and psychological impact (Balen et al., 1995; Teede et al., 2013). Obesity is associated with infertility, miscarriage, obstetric complications (preeclampsia, GDM, thromboembolism, caesarian section), and adverse neonatal outcome (congenital anomalies, a metabolic disease in later life) (Cedergen et al., 2004). Obese patients tend to respond less to ovarian stimulation, requiring higher doses of gonadotropins with no negative association with pregnancy rates (Mulders et al., 2003). Fertility rates are lower with obesity, but ovulation rates have been shown to increase with lifestyle interventions. In overweight women, a moderate weight loss of 5-10% exhibits significant benefits (Kiddy et al., 1990; Radon et al., 1999). Hyperandrogenism, insulin resistance, ovulation, menstrual cyclicity, fertility, abdominal fat, lipid profiles, cardiovascular, DMII, and psychological are demonstrated to improve when weight loss is implemented in overweight women. (Moran et al., 2003; Stamets et al., 2004). Overall, regular monitoring of weight excess and maintaining a healthy BMI is recommended from as early as adolescence.

The composition of dietary interventions for women with PCOS is under investigation. There is limited or no evidence to support the superiority of a particular dietary plan to address these groups' particular requirements (Moran et al., 2013). Certain vitamin deficiencies, such as vitamin D and folic acid, need to be assessed and supplemented as they may have an impact on the reproductive outcome (Balen et al., 2016). General healthy balanced eating is encouraged not only during infertility treatments and efforts to conceive but as a lifelong commitment. For overweight and obese individuals, a low glycemic dietary approach is necessary. An energy deficit diet of 30% of daily caloric intake or 500-750 kcal/day could be prescribed, taking into consideration individual energy requirements, starting body weight, and physical activity level (Costello et al., 2018). Any dietary weight loss approach should be flexible and tailored to individual preferences and needs in order to achieve long-term compliance.

Exercise alone improves insulin resistance (Harisson et al., 2012). Regular, moderate exercise, 3 to 5 times a week, reduces DMII and cardiovascular disease risk in the general population (Shephard and Balady, 1999). High-risk groups may also benefit from resistance or weight-
bearing alone or combined with aerobic work-out (Cuff et al., 2003). For adults 18 - 64 years of age, BMI <25 kg/m², for the prevention of weight gain and the maintenance of good health, a minimum of 150 min/week of moderate physical activity or 75 min/week of vigorous intensity, including muscle strength training x2/week is recommended (Teede et al., 2018). The intensity and duration of exercise required are increased when moderate weight loss is required and modified when it comes to adolescents, as shown below (Figure 6).

![Figure 6. ASRM exercise recommendations for women with PCOS.](image)

**4b. Ovulation induction**

Initial lifestyle alterations have a dual purpose; to induce spontaneous ovulation by the normalization of metabolic and endocrine parameters and to optimize individual general health status before any further intervention. Once first-line measures have failed to restore reproductive potential, ovulation induction methods, using clomiphene citrate (CC), aromatase inhibitors, and metformin, are employed. Ovulation induction aims to induce unifollicular ovulation while avoiding multiple gestations and OHSS. Tubal patency and semen analysis should be considered before ovulation induction if other factors of infertility are suspected (Teede et al., 2018).

**Clomiphene Citrate**

Clomiphene citrate has tissue-specific estrogenic and anti-estrogenic properties. In the hypothalamus, it depletes Estrogen Receptors, thus blocking the negative feedback loop of circulating estrogens. Increased hypothalamic pulse frequency, in turn, increases the secretion of FSH from the anterior pituitary gland promoting follicular growth. Its anti-estrogenic effect is responsible for its typical side effects of hot flushes and breast tenderness, dizziness, nausea, and visual disturbances.
CC has been traditionally used as first-line therapy for anovulatory PCOS (Homburg et al., 2010; Fauser et al., 2012; Balen et al., 2016). CC is usually started on the second day of the cycle, at 50mg/day for five days. In case of resistance to CC, the daily dose should be increased (max 100mg/day) after two cycles because only 75% of the women who will respond to CC will do so in the first cycle. Higher doses do not seem to be beneficial except for reports on high doses being prescribed to obese patients (Homburg et al., 2010). Except for obesity, hyperandrogenism and hyperinsulinemia could lessen the response to CC (Imani et al., 1998). When CC resistance arises, aromatase inhibitors, gonadotropins, and ovarian drilling are alternative options. If, however, there is a high response, the dose can be reduced to 25 mg/day. CC is associated with a 73% ovulation rate, a 36% pregnancy rate, and a 29% live birth rate over six months. The low pregnancy rates compared to high ovulation rates achieved could be attributed to the impaired endometrial development and abnormal cervical secretion as a consequence of the anti-estrogenic effect of CC on the endometrium and the cervix. Thin endometrium, <8 mm, is considered a poor prognostic factor for attaining pregnancy (Homburg et al., 2010). Another cause could be the concomitant release of LH with FSH, which, combined with already high basal LH levels, especially if still elevated after Day 8, could hinder ovulation and pregnancy (Shoham et al., 1990). Most pregnancies are achieved within six treatment cycles, ¾ of them in the first three cycles (Kousta et al., 1997; Homburg, 2010). In the case of pregnancy failure, IVF treatment should be offered. CC has an 11% risk of multiple pregnancies (Kousta et al., 1997). Careful monitoring with TVUS is highly recommended in order to monitor responsiveness and endometrial thickness to ensure therapeutic efficacy, patient safety, and lower the risk of multiple gestations. Additionally, closer monitoring enables better timing of intercourse or intrauterine insemination. The administration of external triggering does not improve pregnancy rates, according to Agarwal and Buyalos, 1995.

**Aromatase inhibitors - Letrozole**

AIs were traditionally used for the treatment of hormone-responsive advanced breast cancer. They inhibit the aromatization of androgens into estrogens. The hypothalamic-pituitary axis is released from the negative estrogen feedback, leading to increased follicular growth. The increase in intra-follicular androgens enhances early follicular growth. Due to their short half-life, their lack of effect on central or endometrial E Receptors and the maintenance of ovarian/pituitary feedback, they exhibit a more favorable side effect profile, with improved
endometrial thickness and less multiple pregnancies compared to CC (Holzer et al., 2006; Homburg et al., 2010, Teede et al., 2018). A 2005 ASRM abstract, by Biljan, raised questions about letrozole’s safety, suggesting a higher teratogenic risk. However, the methodology of the paper was questionable and further studies demonstrated that letrozole might not be associated with increased risk of fetal anomalies (Tulandi et al.; Forman et al., 2007), results in low anomaly rates (Legro et al., 2014) and exhibits no differences in the congenital anomalies when compared to CC and Gonadotropins (Diamont et al., 2015).

Letrozole’s starting dose is 2.5 mg/day taken once daily for five days. The dosage can be titrated up to 10 mg in subsequent induction cycles. It is well-tolerated, with hot flushes, headache, back pain, and nausea being among its most common side-effects.

A multicenter, double-blind RCT and a 2014 Cochrane review of 26RCTs examined the efficacy of letrozole with the classic use of CC, placebo or ovarian drilling and letrozole had higher cumulative ovulation (Legro et al., 2014), clinical pregnancy and live birth rates (Legro et al., 2014; Franik et al., 2015). There were no differences in pregnancy loss, multiple pregnancies, and OHSS rates. A 2018 substantive update of the 2014 review incorporated additional high-quality studies that revalidated previous findings (Franik et al., 2018).

In conclusion, letrozole is safe, effective, and recommended, where available and permitted, as first-line therapy (Teede et al., 2018) or second line in CC resistance (no ovulation) or failure (no pregnancy) (Balen et al., 2016).

**Metformin**

Metformin is a biguanide anti-hyperglycemic agent, currently considered as a first-line oral medication for the treatment of DMII patients, particularly those who are overweight. Metformin has hepatic and peripheral insulin-sensitizing effects suppressing hepatic gluconeogenesis. Could metformin improve fertility in PCOS anovulatory women? Its effect on hyperinsulinemia is evident; studies have shown an indirect anti-androgenic effect in PCOS patients with insulin resistance, reducing androgens up to 50% (Nikolakis et al., 2019). There is evidence of its beneficial effects not only on long term health but also on acting directly or indirectly within the ovary (Diamanti-Kandarakis et al., 2010) affecting oocyte competency (Huang et al., 2015).
According to the 2017 ASRM practice guideline, based on the systematic review of the literature available on metformin studies in PCOS, women concluded that metformin should not be used as a first-line treatment for ovulation induction. Metformin alone increases ovulation rates without significant improvement in pregnancy or live birth rates (Fleming et al., 2002; Tang et al., 2006). When compared to CC, ovulation rates are lower with metformin than CC alone (29% vs. 49%), and live birth rates do not improve (Legro et al., 2007; Zain et al., 2009). There is good evidence that metformin in combination with CC improves ovulation and clinical pregnancy rates but does not improve live-birth rates compared with CC alone in women with PCOS (Legro et al., 2007; Zain et al., 2009; Ayaz et al., 2013). Pregnancy rates seem to increase when metformin is co-administered in CC-resistance cases but further studies to explore which subgroup would benefit the most. Although there is no synergistic effect of metformin with other lifestyle changes, there is moderate evidence from one RCT that pre-treatment with metformin for at least three months followed by the addition of another ovulation-inducing drug increases live-birth rate (Morin-Papunen et al., 2012). There is good evidence that metformin alone does not increase the risk of higher-order pregnancies. Although metformin is considered safe during pregnancy (FDA category B), there is insufficient evidence to support its continuation during pregnancy for reducing the chance of miscarriage. Lastly, more high-quality studies are required to assess the efficacy of metformin according to BMI.

**Gonadotropins – Laparoscopic ovarian drilling**

Ovulation induction with gonadotropins is indicated as second-line pharmacological therapy when first-line oral induction has failed, in women with anovulatory PCOS and no other infertility factors. The use of gonadotropins requires expert and close monitoring, with cost and availability that need to be taken into consideration. The risk in using gonadotropins is multifollicular growth, resulting in multiple pregnancies with the associated increased maternal and perinatal mortality and morbidity and OHSS. OHSS is a potentially life-threatening complication caused by the exaggerated release of VEGF, a vasoactive compound, triggered by endogenous or exogenous hCG, resulting in increased vascular permeability, leading to extravasation of fluid into the third space with subsequent ascites/pleural effusion thromboembolism and hemoconcentration. OHSS is rarely seen in ovulation induction with CC and letrozole; it requires careful monitoring and appropriate starting dose.
For monofollicular development, either a low dose step-up (White et al., 1996) or a step-down protocol is used (Van Sandbrink et al., 1995). The low step-up regime commences with a starting dose of 50-75iu/day and is increased slowly (Orvieto and Homburg, 2009), over a lengthy period of 28-35 days. The step-down protocol utilizes a higher initial dose of 150iu for 3-4d to achieve follicular recruitment, which is then reduced to 50-75 IU. Any available gonadotropin preparation can be used as there is no difference in clinical efficacy, so the most cost-effective preparation should be used (Nugent et al., 2000; Teede et al., 2018). Metformin co-administration could be used in anovulatory PCOS patients with CC-resistance, as there is evidence of higher clinical pregnancy and live birth rates (Bordewijk et al., 2017). Once the leading follicle is at least 17 mm, ovulation is triggered with HCG s/c injection. According to the Greek legislation governing human Reproduction, for women less than 35 years of age, triggering is allowed up to three follicles and E_2 levels less than 800 - 900 pg/ml and for patients between 36-39 years old up to 5 follicles and E_2 lower than 1200 - 1500 pg/ml. For women above 40, the decision making is up to the IVF physician and the couple after obtaining informed consent. In the case of supernumerary follicles, the cycle is canceled, and the couple is advised to refrain from intercourse. (Balen et al., 2016). In some cases, rescue IVF, with possible agonist triggering, oocyte pick up, and vitrification of embryos could be offered when cost and availability is not an issue.

Laparoscopic ovarian “drilling” is another second-line measure in case of OI resistance to CC or letrozole along-side gonadotropin therapy, particularly for those with raised basal LH levels. The procedure needs to be carried out with care and to be as minimally as required to reduce ovarian damage, adhesion formation, and significant adverse effect on ovarian reserve (Balen et al., 2016).

4c. In vitro fertilization - IVM

When first- and second-line interventions have failed to induce ovulation and achieve clinical pregnancy and live birth, controlled ovarian stimulation and in vitro fertilization, if not otherwise previously indicated, can be offered as a third-line treatment. Careful daily dosage selection and extra vigilance during stimulation are required to avoid excessive hyperstimulation and promptly recognize early OHSS signs and symptoms.
Currently, short antagonist protocols are usually implemented due to their patient-friendly profile and the option for agonist triggering, which in combination with a freeze-all strategy, eliminates severe OHSS incidence (Teede et al., 2018). Vitrification and frozen embryo transfer at a subsequent cycle seem to lead to better live birth rates. A recent multicenter randomized control trial demonstrated significantly higher live birth rates and lower pregnancy loss and OHSS rates when comparing fresh to frozen embryo transfer in women with PCOS (Chen et al., 2016), validating the conclusion of previous observation studies (Kansal et al., 20011). On the downside, it showed an increased risk for pre-eclampsia amongst the frozen transfer group with an incidence of 4.4% versus 1.4% in the fresh ET, which should not be overlooked. Metformin could improve the clinical pregnancy rate and reduce the risk of OHSS and should, therefore, be considered as an adjuvant treatment before and/or during COH (Teede et al., 2018). Single embryo transfer ensures singleton pregnancies avoiding the associated perinatal risks and financial consequences.

Lastly, In Vitro Maturation could be offered to couples who are unable to conceive despite the interventions mentioned above due to an increased number of immature oocytes (Teede et al., 2018). In this case, oocytes from non-minimally stimulated cycles are retrieved without triggering and cultured and matured in vitro. Studies have suggested that the cumulative pregnancy by IVM is comparable with that of other PCOS women undergoing conventional IVF (Cha et al., 2005; Soderstrom-Anttila et al., 2005). However, subsequent studies have commented upon potential deleterious effects of IVM on both spindle formation and chromosomal configuration (Navarro et al., 2007,2009; Nichols et al., 2010), which could account for the discrepancy in overall clinical outcome observed after IVM in favor of in vivo maturation. By a recent Cochrane systematic review by Siristratidis et al., 2018, concludes that there is no evidence to propose IVM before IVF therapy.
Conclusions

PCOS is an endocrine, multifactorial disease exhibiting a spectrum of phenotypes. The impact on a woman's wellbeing is variable and evolves throughout her life. A prompt and accurate diagnosis is imperative. The broad implementation of the Rotterdam criteria ensures early recognition, and a multidisciplinary team approach warrants holistic management of the reproductive, metabolic, and psychosocial sequelae of the syndrome. A better understanding of the pathophysiology underpinning PCOS multi-system dysfunction could help optimize individualized interventions optimizing ovulation, oocyte developmental competence, and live birth rates while promoting a healthier lifestyle, free of the associated long-term comorbidities for both the mother and her offspring.
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Appendices

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