Fertility of women with polycystic ovary syndrome in late reproductive age

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Abstract

Background: Age is regarded as a key factor in women's fertility and the main predictor of ovarian reserve. Declines in oocyte number and quality (i.e., "ovarian aging") are primary reasons for deteriorating reproductive outcomes with advancing female age. After the age of 35, woman's fertility declines. Age-related infertility is one of the biggest challenges in reproductive medicine; even with assisted reproductive technologies the live-birth rate in women ≥40 years is still very low per treatment cycle. However, not all women of the same age have identical ovarian reserves. By the opinion of some researchers, achievable pregnancy and live birth rates in advanced-aged women is frequently underestimated. Polycystic Ovary Syndrome is the most common reproductive pathology which is associated with reduced fertility, pregnancy complications and adverse neonatal outcome as well. Several studies suggest that symptoms of polycystic ovary syndrome tend to improve after the age of 40. Hormone levels begin to rebalance, ovulation may restart and therefore, women with polycystic ovary syndrome might have a better ovarian reserve in late reproductive age than women without this syndrome. As a consequence, it might make it easier to achieve pregnancy. Thus, it is hypothesized by several authors that age-related decline in fertility is slower in women with polycystic ovary syndrome. However, the influence of age on other fertility outcomes (clinical pregnancy and live birth rates) is not clear. It is also unclear whether the influence of age-related decline on fertility treatment outcomes is different in women with polycystic ovary syndrome than in those without this disorder. Due to the complexity and heterogeneity of polycystic ovarian syndrome many women with fertility problems remain underdiagnosed. Effective understanding and dissemination of evidence-based management of this disorder is therefore vital. Frustratingly, the research and literature addressing the issue of fertility status of women with polycystic ovary syndrome in late reproductive years is scarce and controversial.

The main goal of our study is to overview the current literature on the fertility status of women with polycystic ovary syndrome in their late reproductive age and describe the potential pregnancy complications in this group of women. We also aimed to highlight the various pathologies that are associated with polycystic ovary syndrome, discuss their key metabolic molecular pathways and explore their impact on fertility.

Search strategy: Literature search was performed through databases of PubMed, Web of Science, Medline, Embase and Cochrein Library, using appropriate search terms alone or in combination. There were no date and language restrictions. We have also searched relevant articles from the list of references. **(TCM-GMJ March 2023; 8 (1):P36-P42)**

Keywords: Polycystic ovary syndrome; Fertility; Metabolic syndrome; Pregnancy complication; Late reproductive age; Live birth rate.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine pathology in women of reproductive age, causing significant health consequences, impairing women's quality of life and fertility. PCOS is characterized by the complexity and heterogeneity of reproductive, endocrinological, metabolic and psychological dysfunctions. It is the major cause of anovulatory infertility and accounts for ~80% of cases in this group of women (1,2,3). In the past decades several attempts have been made to establish diagnostic criteria of PCOS. Initially, a subset of criteria was suggested by the National Institute of Health at the 1990 meeting (4), considering both clinical/biochemical hyperandrogenism and chronic anovulation for the diagnosis. In 2006, by the experts of the Androgen Excess Society (AES) were revised all the data published on PCOS in order to simplify diagnosis (5,6). The AES criteria require clinical and/or biochemical hyperandrogenism simultaneously with oligo/anovulation and ultrasonographic appearance of polycystic ovaries. Currently, diagnosis of PCOS is based on the criteria of the ESRHE/ASRM Rotterdam consensus meeting in 2003 (7). It is based on at least two of the following features: 1. oligo/anovulation; 2. hyperandrogenism: clinical (acne, hirsutism, male pattern alopecia) or biochemical (elevated serum testosterone level); 3. Polycystic appearance of ovaries by ultrasound investigation: ≥12 follicles measuring 2-9 mm in diameter or increased ovarian volume, ≥ 10 cm3. Exclusion of other forms of menstrual disturbances and

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hyperandrogenism is mandatory. However, the Rotterdam consensus has its own restrictions: it may fail to differentiate between PCOS and other ovulatory dysfunctions (OD) (4,8). In young populations irregular menstrual cycles and multicystic ovaries are more common due to hypothalamic -pituitary-ovarian function's immaturity and represent the part of normal, physiological puberty. Therefore, the differential diagnosis in this age group remains even more challenging (1,2,4,8).

According to the characteristic features of PCOS up to 16 phenotypes may exist with different metabolic events and reproductive consequences, however, mainly 4 phenotypes of this heterogenous disorder are established: 1.Phenotype A: Hyperandrogenism (HA)+Ovulatory dysfunction (OD)+Polycystic ovarian morphology (PCOM); 2. Phenotype B: HA+OD; 3. Phenotype C: HA+PCOM; and 4.Phenotype D: PCOM+OD (3,4,5,9). Existing diagnostic criteria are not valid in early and late reproductive years of PCOS women, as they may require different treatment approaches; thus, physician awareness and clinical judgment are the most important factors in the diagnosis of PCOS. In 2018, Teede et al. proposed a comprehensive international guideline for the assessment and management of PCOS, which is based on previous high-quality guidelines and provides a valuable source of evidence-based recommendations to apply into clinical practice (10).

An overall prevalence of PCOS is similar in all countries and varies from 1% to 19% among women of reproductive age depending on the diagnostic criteria used and the race/ethnicity of the population studied (1,2,3,9). By some authors PCOS affects up to 21% of women in high risk groups (11). According to one study, the prevalence of PCOS among Caucasian women varies from 4.7 % in Alabama, to 6.5 % in Spain and 6.8 % in Greece (5). It is as low as 2,2% in the population of Chinese women, and as high as 14% in Iranian women (12). The varying prevalence of PCOS may be due to environmental and socioeconomic factors as well (diet, physical activity/sedentary lifestyle, alcohol/tobacco consumption), which can lead to hormonal alterations or activate a genetic predisposition for the development of PCOS (4,9,10).

Aetiology and pathophysiology of PCOS

The aetiology of PCOS is not clearly understood. It is regarded as a complex, polygenic, multifactorial disorder with endocrine, genetic, metabolic abnormalities involved. Lifestyle and environmental factors play an important role as well (5,9). Although PCOS is defined as a genetically determined ovarian pathology characterized by overproduction of androgens, the pattern of its inheritance is not yet well established. The main candidate genes are supposed to be the key genes encoding factors responsible for the synthesis, transport and regulation of androgens, folliculogenesis and the metabolism of insulin (1,3,5).

Some observations indicate that exposure of the fetal hypothalamus-pituitary-ovarian axis to androgen excess may trigger a chain of reactions that could contribute to the onset of PCOS at puberty. An excess of androgens is more likely to be of fetal origin in response to maternal hCG in females genetically predisposed to PCOS (1,5,9). Environmental conditions (pre- and postnatal) are also thought to activate existing predisposing factors and trigger all the characteristic hormonal and metabolic dysfunctions of PCOS. Oxidative stress and low-grade inflammation play also a role in the pathophysiology of this syndrome. It has been suggested that decreased mitochondrial oxygen consumption, elevated level of reactive oxygen species and inflammatory microenvironment finally contribute to the cell damage, mitochondrial dysfunction and poor oocyte quality in PCOS patients (9,15). It seems likely that epigenetic mechanism may also occur in PCOS. Particularly, in utero exposure to hyperandrogenism may lead to epigenetic reprogramming of anomalies in fetal reproductive tissues, which is manifested as a PCOS phenotype in adulthood. When such epigenetic alterations occur in the germ cell line, transmission of the PCOS phenotype through the several generations is promoted (5,9).

The pathophysiology of PCOS is still controversial. Abnormalities in gonadotropin secretion/action, ovarian folliculogenesis/steroidogenesis, insulin secretion and adipose tissue function, among others, have been described in PCOS. It is suggested that PCOS is a consequence of a vicious circle of androgen overproduction favoring abdominal/visceral fat deposition, that induces insulin resistance (IR) and compensatory hyperinsulinemia, which further facilitate androgen hypersecretion by the ovaries and adrenal glands (1,3,9).

It is now widely accepted that IR, manifesting not only in obese/ overweight women, but also in lean PCOS women, is one of the key pathways to this heterogenous disorder. IR and compensatory hyperinsulinemia are triggering factors for developing hyperandrogenism by acting together with luteinising hormone (LH), on ovarian steroidogenic enzymes and on sex hormone binding globulin (SHBG) production by liver (2,5). This vicious circle in combination with hypothalamic-pituitary dysfunction, an elevated serum LH level, disturbed LH/FSH (follicle stimulating hormone) ratio leads to ovarian dysfunction and finally results in anovulatory infertility, accounting for ~80% of all PCOS cases (3,11,15). As researchers suggested, hypersecretion of LH in these women may trigger early luteinisation of granulosa cells and consequently result in early growth arrest of antral follicles. LH might also stimulate premature meiotic processes which contribute to the impaired oocyte quality and embryonic aneuploidies (5). However, it is not yet clear whether alterations in the hypothalamo-pituitary axis of PCOS patients is primary or secondary to the changes in steroid hormones secretion.

All these pathogenic mechanisms predispose the women with PCOS, especially in late reproductive years, to some metabolic, cardiovascular and psychosexual disorders, which might have serious health consequences and even be life-threatening (2,3,7,9).

Clinical features of PCOS Reproductive

Infertility due to anovulation is a dominant presenting feature of PCOS making this syndrome the most common cause of anovulatory infertility. Ovulatory dysfunction is reported to account for 70-80 % of cases in this group of women (1,2,3,5). A large community-based cohort study found infertility in 72% of women with PCOS compared with 16% in women without PCOS (13). Evidence indicate that pregnancy outcomes in PCOS women, treated even with the assisted reproductive technologies (ART), remain less than satisfactory (14,15).

Beside the infertility, other pathologies, such as oligo/amenorrhoea, irregular or heavy menstrual bleeding, hirsutism, acne, alopecia, obesity, disturbed psychosexual mood are included in the spectrum of reproductive disorders. However, many women show regular cycles in the beginning of their reproductive life which further continue on to become oligomenorrheic (9,11,13,14). Menstrual irregularities often appear after menarche and begin to normalize close to menopause. This correlates to a decrise in androgen level with advancing age in women with PCOS (2,5).

It has been suggested that women with PCOS had a significantly increased risk of spontaneous abortion compared with non-PCOS women (25% vs. 18%, P<.01)(11). Authors pinpointed that these women have particularly a greater risk of early miscarriage following euploid embryo transfer, independently of age and BMI. Other pathological conditions, such as gestational diabetes, hypertension, preeclampsia, preterm birth, large/small- for-gestational-age neonates and macrosomia are also frequent complications of pregnancy in PCOS women. Alterations of uterine vasculature reported in these women can determine non-adequate trophoblastic invasion leading to defective placentation and unfavorable outcome of pregnancy (11,15,16).

In normal condition, the androgens are rapidly converted to estrogens by placental aromatase. In PCOS this process is inhibited by insulin. Furthermore, the expression of androgen receptors is considerably increased in the placenta of women with PCOS. Maternal and placental hyperandrogenism may contribute to an increased risk of preeclampsia, vasoconstriction, thrombosis and consequently, to pregnancy loss (2,5,8).

Some authors hypothesized that the endocrine dysfunction in PCOS patients caused impaired endometrial receptivity, which leads to defective decidualization and aberrant endometrium during pregnancy (15,16). Women with PCOS due to prolonged exposure to unopposed estrogens are also at higher risk of developing endometrial hyperplasia and even cancer, which can further alter endometrial receptivity reducing the chances for successful pregnancy (5,9,15).

Although the fine mechanisms of pregnancy complications in PCOS is not completely understood, they may be linked to hyperandrogenism, obesity, insulin resistance, placental dysfunction and infertility treatment as well. Two meta-analyses, based on retrospective studies demonstrated that a 3-4-fold increased risk of pregnancy-induced hypertension and preeclampsia, a 2-fold increased risk of preterm delivery and a 3-fold increased risk of gestational diabetes can be observed in women with PCOS (17,18). It is noteworthy that, a large proportion of the published studies on pregnancy complications in PCOS women do not distinguish neither between different PCOS phenotypes nor adjust for other possible confounders (BMI, parity). This make difficult to establish causal relations between PCOS and adverse pregnancy outcomes (14).

The clinical manifestations of PCOS in perimenopausal women are not well studied. There is a histological evidence that these women have a greater number of antral follicles than healthy fertile women of the same age, and higher serum level of Anti-müllerian hormone. This may suggest prolonged reproductive function and greater ovarian reserves (5,9,15).

Metabolic syndrome

Beside the impaired fertility and obstetric complications PCOS exhibits a wide range of metabolic complexity. The division of PCOS patients into four different phenotypes highlights the existing heterogeneity of this syndrome that further perplexes the differential diagnosis (6,8,9).

PCOS is associated with IR-related metabolic alterations, so-called Metabolic syndrome, including impaired glucose tolerance, insulin resistance, compensatory hyperinsulinemia, early-onset type 2 diabetes, obesity and increased risk of cerebro-/cardiovascular diseases (2,10,15). The central pathways in this syndrome are IR and hyperinsulinaemia. Recent research using WHO criteria for IR, reported that 85% of PCOS women diagnosed by the Rotterdam criteria are affected with this condition (75% of lean and 95% of overweight and obese women) (2,5).

Hyperandrogenism and insulin resistance, main characteristic features of metabolic syndrome in PCOS are associated with alterations in the coagulation/fibrinolytic systems, resulting in endothelial dysfunction, atherothrombosis and chronic low grade inflammation, which may lead to microvasculopathy and placental dysfunction (5,9,17). Vascular disturbances such as intima-media thickness/inflammation, endothelial dysfunction, increased arterial stiffness, are more prevalent in PCOS patients. Around 30 –40% of PCOS women show impaired glucose tolerance and up to 10% develop type 2 diabetes mellitus by the age of 40. The phenotype with hyperandrogenemia and IR seems to be linked with a higher metabolic risk (9).

All abovementioned metabolic disturbances combined with disordered eating habits and psychosexual features (anxiety and depression, impaired quality of life, body image) further exacerbates reproductive health and other somato-psychological morbidities of women with PCOS.

Impact of maternal age on fertility

Age is a key factor affecting female fertility and the main predictor of ovarian reserve. With advancing age, the reproductive capacity of women declines due to reduced ovarian reserve. Declines in oocyte number and quality, as

well as the increased prevalence of embryonic aneuploidy are primary reasons for deteriorating reproductive outcomes by age. An almost linear decrease in fertility is observed in women ≥35 of age (19). The size of initial follicle pool and the proportion of follicles undergoing atresia or beginning growth are mostly genetically determined. Atresia of follicle pool is accelerated in women over 37–38 years and this in combination with environmental factors, such as cigarette smoking, anticancer treatment, irrational diet, influence the rate of ovarian aging (20,21).

By the rigorous research concerning "ovarian aging", various defective physiological pathways, such as energy production, metabolism, epigenetic regulation, cell cycle checkpoints and increased meiotic missegregation have been clarified, however, the precise molecular and biochemical mechanisms involved in age-related infertility and their impact on oocyte/embryo quality remain to be clearly explained (21). Age affects the quality of germ cells due to aneuploidy and other genetical errors. Its rate is low in the age ≤ 35 (53 % in 3 days embryos), but increases up to 74 % at the age of 41–42, and reaches to 93 % in the age ≥ 42 (22).

Age-related chromosomal abnormalities mainly arise due to meiotic impairments during oogenesis, presented with defective segregation patterns such as non-disjunction, premature separation of sister chromatids or reverse segregation. The most common chromosomal abnormality seen with increasing age is trisomy. One of the important mechanisms of this disturbed chromatin division during the meiosis is thought to be an altered function of oocyte mitochondria, possibly its decreased activity and loss of cellular polarity (21,22). One study evaluating and comparing oocytes from young (20–25 y.) and older women (40–45 y.) revealed that 79% of the older oocytes had meiotic spindle abnormalities vs. 17% in the younger women. Furthermore, the rate of significant chromosomal abnormalities in live births is 1:500 in ≤ 30 age group, 1:80 at age of 35, and 1:20 at age of 45 years. (23).

The selection process of oocytes seems also to become more aberrant with increasing age. Available data from IVF studies show that the selection of oocytes is less discriminating, allowing maturation of follicles, which in younger women would have undergone atresia (22). A study investigating intrafollicular molecular environment in women at different ages, demonstrated that follicular maturation process in older women is accelerated. Gene expression studies by real-time PCR in follicular fluid of granulosa cells, demonstrated in women ≥ 43 of age convincing evidence of premature luteinization of relatively small follicles. In vitro culture of granulosa cells from older women exhibited lower proliferation and increased apoptosis. It has been suggested that prematurely luteinized follicles, in turn, produced "over-mature," poor quality oocytes (24).

Finally, various uterine pathologies, fibroids, endometriosis, chronic endometritis/endometrial polypus and general health conditions (cardiovascular, metabolic and oncological diseases, surgical procedures) can also be considered as oocyte-independent factors, associated with age-related infertility (21,22).

Advanced maternal age ≥ 40 years has been shown to be an independent risk factor for miscarriage, congenital anomalies, gestational diabetes, preeclampsia, placenta previa, placental abruption, preterm delivery, intrauterine growth restriction, stillbirth, and perinatal mortality. One potential explanation for this may be a failure of the uterine vasculature to adapt to the increased hemodynamic demand of pregnancy. Additionally, older patients are at an increased risk for multiple gestations, increasing the overall rate of perinatal complications (21,23).

The role of anti-Müllerian hormone and antral follicle count in the assessment of fertility in women of late reproductive age.

Anti-Müllerian hormone (AMH) is produced by the ovarian granulosa cells of secondary, preantral and early antral follicles <6 mm in diameter and belongs to the transforming growth factor-β (TGF-β) family. It is a dimeric glycoprotein involved in cell growth/differentiation process and its secretion ceases as follicles grow into dominance. The main physiological role of AMH in the ovary seems to be the inhibition the development of early stages follicles and prevention of the recruitment of nondominant follicles (22,23,24).

Antral follicle count (AFC) determines all follicles with a diameter 2-10 mm in the early follicular phase. Histologic studies have found that AFC correlates with the number of remaining primordial follicles. If AFC < 3 to 10 total follicles, it has been associated with reduced success in achieving pregnancy following ART. An AFC < 3 to 4 follicles has a sensitivity of 9-73% and a specificity of 73-100% for predicting poor ovarian response to stimulation. Thus, AFC is appropriate tool to identify patients with possible poor response to stimulation with ART (23).

Serum AMH level is age-dependent. It declines with advancing female age and this decrease may be occur before alterations in other age-related variables of female reproductive system. The concentration of AMH is proportional to the number of developing follicles and correlates with ovarian reserve. By several researchers was shown that this correlation was stronger than with any other hormonal markers (inhibin B, E2, FSH). Therefore, AMH has emerged as a sensitive, reliable indicator of ovarian reserve and surrogate marker of reproductive aging since 2002 (20,22,23).

AMH is not dependent on the day of cycle. As serum AMH declines with increasing age, its value < 0.7 ng/mL has been correlated with decreased fecundability in natural cycles and poor ovarian response to stimulation with ART. Cutoff values between 0.2 and 0.7 ng/mL have a sensitivity of 40-97% and a specificity of 78-92% in predicting poor ovarian response to stimulation (23).

Assesment of ovarian reserve is recommended for patients who are at risk of diminished ovarian reserve. Although the level of AMH is regarded as a good predictor of oocyte quantity, it does not provide information about the quality of oocyte. Thus, it is possible that woman with low serum AMH level

and reduced number of oocytes might have normal, age-appropriate oocyte quality.

In women with PCOS, serum AMH level tend to be elevated, possibly due to the higher number of follicles, hyperproduction of AMH by granulosa cells and hyperinsulinemia. The positive correlation between AMH and fasting insulin levels may be explained by the aberrant impact of insulin on granulosa cells or by the hyperandrogenemia in response to elevated insulin level (3,5,8). With the overproduction of AMH its counteracting/inhibitory effect on FSH might lead to anovulation, and there have been studies correlating AMH level with ovulatory dysfunction in PCOS women (8).

Although promising, AMH level has not been established as a diagnostic criterium for PCOS and its exact value remains still unclear. By Le et al., the value of serum AMH has been found not considerably superior to LH/FSH ratio in PCOS diagnosis. The researchers suggested that the combination of different parameters including AMH, LH and LH/FSH ratio together with clinical characteristics may be helpful to establish the diagnosis of PCOS (25).

Taking into account all of the above mentioned, tests for the assessment of ovarian reserve should be interpreted with caution. Abnormal results do not define infertility, particularly among young women. The prognostic value of such tests mainly depends on woman's age. However, abnormal tests indicate a need for further deepened evaluation and more extensive approach in management.

Impact of aging on women with PCOS in late reproductive years.

It has been suggested that despite the heterogeneity in phenotype and morbidity, women with PCOS appear to have an advantage in ovarian reserve. Both population- and clinic-based studies have shown that fertility window may be extended in women with PCOS. Favorable ovarian reserve in these individuals ≥ 35 years of age is obvious. However, whether this advantage in aged PCOS population, especially in ≥ 40 age group leads to better success in live births is controversial. Continuous attrition of oocytes and compromised oocyte quality, alongside with cumulative adverse reproductive tract factors undoubtedly limit the success of infertility treatments in women ≥ 35 years of age. Therefore, the fertility of women with PCOS ≥ 35 years of age is a significant concern (19,20,21,26).

Analysis of ovarian cortical biopsies of women with PCOS show a six-fold increased density of primordial and primary follicles compared with women without this syndrome. These findings suggest that larger ovarian reserve associated with PCOS may be either due to increased initial number of germ cells or a decrease in the loss of these cells. Surrogate markers of ovarian reserve such as AFC and serum AMH levels are also increased in PCOS women in comparison with in age-matched controls and, moreover, their level is stable, regardless of age (21,26). A long-term follow-up study reported that AMH level and AFC were significantly higher in PCOS women than in non-PCOS controls, and the differences remained beyond 35 years of age (27). Therefore, the advantage of ovarian reserve in aged PCOS women may indicate a significant ovarian response; consequently, adequate number of retrieved oocytes might provide considerable number of embryos for selection, resulting in pregnancy and LBR.

These findings have led to the suggestion that reproductive window may be prolonged in PCOS women. Some researchers hypothesized that the greater number of antral follicles and higher AMH levels may represent a reproductive advantage in PCOS patients undergoing IVF procedure. However, it is highly controversial whether these findings are applicable for counseling women with PCOS considering their fertility potential, especially in the fourth decade of life (20,26).

A retrospective cohort study demonstrated that retrieved oocytes and live birth rate remained stable in the group of PCOS women, but decreased in age-matched controls in the age group of 22-41 years (20). Contrast findings were reported by another large-scale study, which assessed whether the women with PCOS follow the same age-related decline in IVF treatment outcomes compared with normo-ovulatory controls, and also, to evaluate in ≥ 40 of age PCOS women possible lengthening of the reproductive window (26). Authors demonstrated ~30% reproductive advantage in the number of oocytes and clinical pregnancy/ live-birth rates in PCOS women as compared with control group (women with tubal factor infertility) until the age of < 40. There was no significant difference in live-birth rate between these two groups in the age of ≥ 40. The rate of age-related decline in outcomes was similar in PCOS women and those from the control group. These findings did not point out neither prolonged reproductive window for women beyond 40 years of age nor subsequent advantage in clinical pregnancy/live-birth rates. Authors concluded that possibly, the higher oocyte numbers in the fourth decade of life are not able to overcome the age-related effects on oocyte quality. Therefore, as these women do not exhibit any reproductive advantage and the window of treatment may not be extended, it is advisable that infertile women with PCOS should be treated in a timely manner despite the favorable ovarian reserve (26).

Similar results were obtained by the most recent study among the aged PCOS patients compared to control group of women with tubal factor infertility. Guan et al., have found that there was no significant difference between the aged PCOS women (≥35 of age) and controls. The CLBR significantly decreased in women up to 37 years of age. Authors concluded that, despite the higher number of oocytes retrieved, the reproductive window is not extended for PCOS patients compared with control group. Age, AMH and the number of retrieved oocytes play crucial roles in the CLBRs of patients of advanced age (≥35 years) (28).

In contrast to the above mentioned studies, Li et al., reported that age-related decline in treatment outcomes was slower in aged PCOS women (≥40 of age), than in age-matched non-PCOS patients. Particularly: PCOS women ≥ 40 years had a higher implantation rate (27.8 vs. 15.7%, $P < 0.05$), clinical pregnancy rate (51.4 vs. 26.1%, $P < 0.05$), LBR (42.3 vs. 18.2%, $P < 0.05$), and CLBR (50.0 vs. 21.5%, $P < 0.05$) than non-PCOS women over 40 years. These values were comparable between PCOS patients 35-40 years and ≥ 40 years of age

(19). Authors concluded that advantage in fecundity can be expected in PCOS patients even over 40 years old, however, weight loss before IVF treatment may not be helpful in achieving pregnancy and thus, initiating infertility treatment immediately would be essential (19).

Similar results were demonstrated by Mai et al. Researchers showed that age-related decline in AFC and serum AMH in women with PCOS was slower compared to controls, and that these values in PCOS women ≥ 35 years of age were significantly higher than in controls. In the same study authors have found that women with PCOS ≥ 35 years of age experienced a higher cumulative live birth rate (CLBR) over two years compared with age- and BMI-matched tubal factor controls. Investigators explained this by favorable oocyte reserve and more available embryos in comparison with controls, which overcome the compromised oocyte quality in aged PCOS women (27). Hwang et al. reported that, when compared in age-subgroups, pregnancy and LBR remained stable in PCOS women <38 years of age, while parameters declined significantly with age in tubal factor controls (29).

The discrepancies among studies may be due to the different age groups included in investigations. The heterogeneity of PCOS phenotypes may also have distinct influences on outcomes: it is reported that hyperandrogenic PCOS phenotypes have significantly lower CLBRs than normo-androgenic phenotypes. Finally, accumulating evidence indicates significant and adverse effects of female obesity on IVF outcomes. Many studies controlled investigating groups only for age and do not take into account confounding bias caused by BMI, which may lead to different results and scientific conclusions (27).

Concluding remarks

Nowadays, in modern society there is a strong tendency toward delayed childbearing. Therefore, oocyte factors (decline in oocyte quantity and quality) are the main causes responsible for decreased fertility of women in late reproductive age. Even though PCOS patients have favorable ovarian reserve, maternal age is still the strongest predictor of success among these women. Compromised oocyte quality and cumulative adverse metabolic events inevitably limit the success of ART in PCOS women, especially ≥ 35 years of age. However, the fine molecular and biochemical mechanisms which impact on oocyte quality remain to be clearly elucidated. Therefore, evidence-based data should always be used for the counseling of aged PCOS patients. An early and precise diagnosis is important for an ade-

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