FROM PATHOPHYSIOLOGY TO POTENTIAL INTERVENTIONS: INVESTIGATING THE INTRICATE DYNAMICS OF POLYCYSTIC OVARY SYNDROME, AGING, AND FERTILITY

Plamena Kabakchieva1 https://orcid.org/0000-0003-3577-0577

1Clinic of Internal Medicine, Naval Hospital Varna, Military Medical Academy, Bulgaria

Received: August 14, 2023
Accepted: September 20, 2023

Corresponding author: Kabakchieva Plamena, E-mail: plamenakabakchieva@yahoo.com
Twitter handle: @PKabakchieva

Abstract
Polycystic ovary syndrome (PCOS) and age-related decline in fertility are complex issues affecting women’s reproductive health. This review aims to explore the intricate dynamics between PCOS, aging, and fertility, and examine potential interventions for improved clinical outcomes. It delves into the pathophysiology of PCOS, highlighting hormonal imbalances, metabolic disturbances, and the impact on ovarian function and follicular development. Concurrently, age-related changes in female fertility are discussed, including ovarian reserve decline, hormonal shifts, and alterations in egg quality and uterine environment. Emphasizing the overlapping mechanisms, shared pathways are elucidated such as hormonal dysregulation, insulin resistance, hyperandrogenism, and inflammation. Additionally, the clinical implications of diagnosing and managing PCOS in aging women are addressed, as well as fertility preservation options and assisted reproductive techniques. Furthermore, potential interventions and therapeutic strategies are explored, encompassing lifestyle modifications, pharmacological interventions, and emerging technologies. By comprehensively reviewing the current evidence and research gaps, this article provides valuable insights into the interplay between PCOS, aging, and fertility, paving the way for optimized clinical approaches and future advancements.

Keywords: polycystic ovary syndrome; fertility; aging; pathophysiology.

How to cite: Kabakchieva P. From Pathophysiology to Potential Interventions: Investigating the Intricate Dynamics of Polycystic Ovary Syndrome, Aging, and Fertility. Anti Aging East Eur 2023;2(3):132-142  https://doi.org/10.56543/aaeeu.2023.2.3.02

Key Messages for Research and Practice

- Recognizing the intricate relationship between PCOS, aging, and fertility enables the development of targeted interventions and personalized management plans, ultimately improving the reproductive outcomes of women facing these challenges.

- Exploring the shared hormonal dysregulation, insulin resistance, inflammation, and genetic influences in PCOS and aging sheds light on potential opportunities for intervention guiding the development of innovative therapies and strategies to mitigate the impact of these conditions on reproductive health.

- Women with PCOS, especially those dealing with aging, benefit from a range of fertility preservation options encompassing lifestyle modifications, ovulation induction, and assisted reproductive techniques, to enhance the chances of successful pregnancy and healthy childbirth.

- To optimize clinical approaches and improve reproductive outcomes, early diagnosis and comprehensive care are crucial for women with PCOS as they age.
Polycystic ovary syndrome (PCOS) and age-related decline in fertility present complex challenges in women’s reproductive health. PCOS, a common endocrine disorder, affects approximately 5-18% of women of reproductive age [1]. It is characterized by hormonal imbalances, metabolic disturbances, and reproductive abnormalities, leading to symptoms such as irregular menstrual cycles, ovarian cysts, hyperandrogenism, and insulin resistance [2]. On the other hand, advancing age is associated with a natural decline in female fertility due to changes in ovarian reserve, hormonal shifts, and alterations in egg quality [3].

While PCOS and age-related decline in fertility are often studied independently, there is a growing recognition of their intricate interplay [4] and late-onset consequences [5,6]. Many women with PCOS experience delayed childbearing due to various factors, including delayed diagnosis, subfertility, disrupted sexual behavior, or social factors [7]. Consequently, they often encounter the challenges of trying to conceive at an advanced maternal age, when fertility potential is already diminished [8].

The primary goal of this narrative review is to investigate the complex dynamics between PCOS, aging, and fertility, shedding light on shared mechanisms and potential interventions. By examining the pathophysiology of PCOS and age-related changes in female fertility, the review seeks to identify overlapping factors contributing to reproductive challenges in women affected by PCOS as they age. Furthermore, it aims to explore the clinical implications of diagnosing and managing PCOS in aging women and discuss fertility preservation options and assisted reproductive techniques specifically tailored to this population.

Understanding the intricate relationship between PCOS, aging, and fertility is crucial for optimizing clinical approaches and improving reproductive outcomes in this unique patient population. By synthesizing current evidence, identifying research gaps, and discussing potential interventions, this review provides valuable insights into the multifaceted nature of PCOS, aging, and fertility. Ultimately, this article aims to pave the way for improved diagnostic strategies, personalized management plans, and innovative interventions that can enhance reproductive success in women navigating the complexities of PCOS and aging.

Search strategy

We employed a methodical approach inspired by the recommendations of Gasparyan et al [9]. To ensure comprehensive coverage, a systematic search was conducted in the PubMed (MedLine) and Scopus databases on August 8, 2023 using the keywords «PCOS», «aging», and «fertility.» Following stringent criteria excluding duplicates and irrelevant articles, as well as focusing solely on original research papers, a curated selection of papers was identified for inclusion in the section dedicated to understanding the interplay between PCOS, aging, and fertility. Additionally, diverse review articles, society guidelines and recommendations were incorporated to establish a comprehensive background, drawing from various database searches and the expertise of the author in the field.

Pathophysiology of Polycystic Ovary Syndrome

Definition and Diagnostic Criteria

Polycystic ovary syndrome is a complex endocrine disorder characterized by a combination of clinical, hormonal, and ultrasound features. The diagnostic criteria for PCOS have evolved over time and currently include the Rotterdam criteria, which require the presence of at least two of the following: oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination [10]. This comprehensive definition aims to capture the heterogeneity of PCOS presentations and encompass the varied manifestations of the syndrome.

Hormonal Imbalances and Metabolic Disturbances

PCOS is identified by irregularities in hormones and disruptions in metabolism that contribute to its underlying physiology. Elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio and insulin levels, along with insulin resistance, are commonly observed in women with PCOS [11]. Excessive insulin stimulates ovarian androgen production, leading to hyperandrogenism, which is a hallmark of the syndrome [10]. Hyperandrogenism results in the clinical manifestations of PCOS, such as hirsutism, acne, and alopecia [12]. Moreover, insulin resistance, a key feature of PCOS, is associated with dyslipidemia, impaired glucose tolerance, and increased risk of type 2 diabetes and cardiovascular disease [13]. The intricate interplay between insulin resistance and hyperandrogenism contributes to the vicious cycle of PCOS pathogenesis.
Impact on Ovarian Function and Follicular Development

The process of ovarian follicle development relies on a precise equilibrium between extra- and intra-ovarian factors. PCOS exerts a profound impact on ovarian function and follicular development. Women with PCOS often exhibit anovulation or oligo-ovulation, resulting from disrupted folliculogenesis and impaired maturation of ovarian follicles [14]. The extraovarian factors such as insulin resistance with hyperinsulinemia, metabolic disorders, visceral obesity with impaired secretion of adipokines and myokines, and neuroendocrine disorders [15] alone or in combination worsen the follicular microclimate and, respectively, folliculogenesis and oogenesis. The excessive production of androgens by the ovaries disrupts the delicate hormonal milieu necessary for follicular growth and ovulation [16]. Moreover, androgens encourage the expression of aromatase and, consequently, the LH/chorionic gonadotropin receptor (LHCGR) in granulosa cells. As the follicle matures, androgens seem to limit cell division and encourage cell death. This dual role of androgens was initially observed in a non-human primate where they enhanced FSH effects in smaller antral follicles but hindered them in larger ones [17].

Other intraovarian factors that modulate follicular development and maturation include members of the transforming growth factor-beta superfamily (eg: anti-mullerian hormone (AMH), inhibin, activin, bone morphogenic protein, and growth differentiation factors) [17]. Insulin-like growth factor 1 (IGF-1), various cytokines and steroid hormones are thought to probably also play a role in the abnormal follicular growth and functionality seen in PCOS [17,18]. The oocyte and its surrounding granulosa cells produce many of these intraovarian factors [19], and the good “dialogue” between them is the key mechanism for normal follicular growth [20, 21].

Additionally, this process is affected by the impaired coordination between LH, FSH, IGF-1, AMH, the enzymes involved in androgen conversion, and other putative factors observed in PCOS. An example of this is the fact that follicular resistance to FSH is most likely a secondary manifestation of increased levels of AMH secreted by the large cohort of preantral follicles or of hyperandrogenism in the ovary [22, 23]. All this results in irregular ovulation (oligoovulation) or anovulation and, as the most important consequence, infertility or subfertility [18].

The Role of Inflammation and Oxidative Stress

In recent years, the role of inflammation and oxidative stress in the pathophysiology of PCOS has gained significant attention. Females with PCOS demonstrate persistent, mild inflammation, marked by heightened levels of pro-inflammatory cytokines and enhanced immune cell activity [24]. This chronic inflammatory state contributes to insulin resistance, dyslipidemia, and endothelial dysfunction, further increasing the risk of metabolic complications in PCOS. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, is also heightened in PCOS. Oxidative stress contributes to follicular damage, impaired oocyte quality, and embryo development, thereby impacting fertility outcomes [25].

Understanding the pathophysiology of PCOS is crucial for developing targeted interventions to address the underlying mechanisms driving the syndrome [26]. The hormonal imbalances, metabolic disturbances, disrupted ovarian function, and the involvement of inflammation and oxidative stress collectively contribute to the complex nature of PCOS, highlighting the need for a comprehensive approach to its management and treatment.

Age-Related Changes in Female Fertility

Ovarian Reserve Decline and Follicular Dynamics

Advancing age is associated with a natural decline in female fertility, primarily attributed to the progressive reduction in ovarian reserve and alterations in follicular dynamics [27]. Ovarian reserve refers to the quantity and quality of the remaining follicles in the ovaries, which represent a finite pool of eggs available for ovulation [28]. With age, the ovarian reserve gradually depletes, leading to a decreased number of follicles available for recruitment and development. Additionally, the quality of the remaining follicles may decline, affecting the chances of successful fertilization and embryo development [29].

Hormonal Shifts and Imbalances

Aging is also characterized by hormonal shifts and imbalances that impact female fertility. The hypothalamic-pituitary-gonadal axis, responsible for regulating reproductive hormone production, undergoes changes with age. In particular, there is a decrease in the production of gonadotropin-releasing hormone (GnRH), FSH, and estrogen, leading to altered feedback mechanisms and hormonal imbalances. The reduced estrogen
levels affect the maturation and quality of the developing follicles, thereby influencing ovulation and fertility potential [30]. Separate research endeavors have indicated that key pathways related to reproduction, which encompass AMH, vascular endothelial growth factor (VEGF), neurotrophins, IGF1, and mitochondrial function, play a crucial role in the wholesome development of oocytes and cumulus cells, and these pathways change as age advances [31].

Impact of Age on Egg Quality and Embryo Development

One of the key factors contributing to age-related decline in female fertility is the impact on egg quality and subsequent embryo development. Meiotic mistakes in oocytes due to aging are widely recognized. Equally significant is comprehending the alterations in intraovarian controls as women age, along with exploring potential remedies to counteract the aging effects. The quality of oocytes diminishes due to various factors, including increased DNA damage, impaired chromosomal segregation, failure of spindle assembly, and mitochondrial dysfunction [32–34]. These age-related changes in egg quality lead to a higher risk of chromosomal abnormalities and reduced embryo viability, thereby affecting the chances of successful conception and pregnancy [35].

Changes in Uterine Environment and Implantation Potential

The aging process also affects the uterine environment and implantation potential. With age, the endometrium undergoes structural and functional changes that can impair successful embryo implantation. The alterations in hormone levels, vascularization, and receptivity of the endometrium contribute to reduced implantation rates and an increased risk of pregnancy complications, such as miscarriage and chromosomal abnormalities [31, 36]. Additionally, age-related changes in the cervix and cervical mucus can hinder sperm transport and reduce the likelihood of successful fertilization [37]. Understanding the age-related changes in female fertility is crucial for managing and optimizing reproductive outcomes in women seeking to conceive at an advanced maternal age. The decline in ovarian reserve, hormonal shifts, compromised egg quality, and alterations in the uterine environment collectively contribute to the reduced fertility potential observed with increasing age. By comprehending these changes, researchers and clinicians can develop strategies to mitigate the impact of age on female fertility and improve the chances of successful conception and healthy pregnancies.

Overlapping Mechanisms: PCOS, Aging, and Fertility

Shared Hormonal Dysregulation and Altered Metabolism

Both PCOS and the aging process involve hormonal dysregulation, albeit through different mechanisms. PCOS is characterized by elevated levels of androgens, such as testosterone, as well as imbalances in gonadotropins, insulin, and estrogen. The excessive androgens associated with PCOS tend to ameliorate as women reach middle age, and this sometimes coincides with the restoration of regular menstrual cycles [38]. These changes appear to be linked to the decline in the number of follicles during the transition to menopause, which is accompanied by decreasing levels of serum inhibin-B and rising levels of FSH that uphold the secretion of estradiol [39]. While the hyperandrogenic symptoms might diminish during menopause [38], persistent metabolic dysfunction continues throughout life and might even heighten the risk of cardiovascular disease after menopause [40].

Excessive levels of clinical and biochemical androgens pose a significant issue among young women with PCOS, while the accumulation of metabolic challenges tends to grow as they age. Several cardiovascular risk factors under scrutiny rely on the levels of free androgen index (FAI) and sex hormone-binding globulin (SHBG). Additionally, increased body mass index (BMI) and visceral obesity solidifies their fundamental contribution to the emergence of most metabolic consequences in PCOS and is associated with age. Hence, it is imperative to tackle the control and management of androgen excess and weight gain at an early stage to prevent the onset of metabolic disruptions in women with PCOS [41].

Insulin Resistance and Hyperandrogenism

Insulin resistance and hyperandrogenism are common features in both PCOS and aging. Insulin resistance, characterized by reduced responsiveness of tissues to insulin, is observed in many women with PCOS as well as in aging individuals. Insulin resistance contributes to hyperinsulinemia, which in turn stimulates ovarian androgen production, leading to hyperandrogenism. Similarly, insulin resistance increases with age and can contribute to elevated androgen levels in women as they approach menopause. These shared metabolic and endocrine abnormalities contribute to the pathophysiology of PCOS and add to the overall risk of age-related disorders such as type 2 diabetes, atherosclerosis, depression, and osteoarthritis [5, 42–44].
Inflammation and Oxidative Stress as Common Pathways

Inflammation and oxidative stress have emerged as common pathways linking PCOS, aging, and fertility. In both PCOS and aging women, chronic low-grade inflammation is observed in both PCOS and aging [45, 46]. Increased interleukin-18 levels are associated with various indicators of overall and abdominal fat accumulation as well as insulin resistance among women diagnosed with PCOS [24]. While inflammation can disrupt ovarian function, impair folliculogenesis, and contribute to infertility, inflammation could contribute to cardiovascular risk by increased glycocalyx shedding, endothelial dysfunction, and atherosclerosis initiation [47]. Therefore, suppressing inflammation in patients with PCOS could also have beneficial effects on cardiovascular health, similar to anti-inflammatory therapies in rheumatoid arthritis [48].

Similarly, oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and the body’s antioxidant defenses, is heightened in PCOS and aging. Oxidative stress can damage oocytes, impair embryo development, and negatively impact fertility outcomes. The interplay between inflammation and oxidative stress represents a shared mechanism influencing the reproductive health of young women affected by PCOS, whereas “metaflammation” is playing a crucial role in those undergoing age-related changes [49].

Genetic and Epigenetic Influences

Genetic and epigenetic influences play significant roles in PCOS, aging, and fertility. Genetic factors play a role in shaping and advancing both PCOS and aging, impacting the development and progression of these conditions. Various genetic variants have been associated with PCOS susceptibility and age-related changes in reproductive function. A recent study showed that a genetic variant on chromosome 5 is associated with an increased risk for PCOS in Europeans. This variant affects the RAD50 gene's behavior in the ovary, which is vital for DNA repair [50, 51], influenced by environmental factors and impact the expression of genes involved in PCOS and age-related changes in fertility. On the other hand, DNA repair pathways have been linked to the age at which women experience menopause [52]. This suggests a potential shared mechanism between polycystic ovary syndrome (PCOS), ovarian aging, and the RAD50 gene. However, this connection remains speculative and requires further research to establish its validity [53].

Additionally, epigenetic modifications, which regulate gene expression patterns without altering the underlying DNA sequence, can be influenced by environmental factors and impact the expression of genes involved in PCOS and age-related changes in fertility. For instance, the androgen receptor gene positioned on the X chromosome could potentially be influenced by DNA methylation [54], which functions as the primary mechanism within the domain of epigenetics and has been indicated to have involvement in conditions such as cancer, the aging process, and intricate chronic ailments [55]. The interplay between genetic and epigenetic factors contributes to the overlapping mechanisms observed in PCOS, aging, and fertility.

Understanding the shared mechanisms between PCOS, aging, and fertility provides valuable insights into the complexity of these conditions and their impact on reproductive health. The shared hormonal dysregulation, insulin resistance and hyperandrogenism, inflammation, and oxidative stress, as well as genetic and epigenetic influences collectively contribute to the interplay between PCOS, aging, and fertility (Figure 1). By unraveling these overlapping mechanisms, researchers and clinicians can develop targeted interventions and personalized approaches to optimize fertility outcomes in women affected by PCOS as they age.

Figure 1. Shared features of aging ovary and ovary in women with PCOS
Diagnosis and Management of PCOS in Aging Women

The diagnosis and management of PCOS in aging women present unique challenges due to the overlapping symptoms of PCOS and age-related changes in reproductive function. Diagnosing PCOS in aging women requires careful consideration of clinical and biochemical parameters, taking into account the impact of age-related hormonal shifts and changes in ovarian function. Diagnostic criteria for PCOS, such as the Rotterdam criteria, can still be applied, but with adjustments to account for age-related variations in hormone levels and ovarian morphology. The diagnosis of PCOS is made mainly on the basis of a retrospective history of irregular menstrual cycle and the presence of polycystic ovarian morphology, but in combination with current hyperandrogenism and insulin resistance is certain [56].

The management of PCOS in aging women involves a comprehensive approach that addresses both the symptoms of PCOS and the potential impact of age on fertility. Lifestyle modifications, including weight management, regular physical activity, and dietary interventions, continue to be essential components of PCOS management. Additionally, optimizing metabolic health and managing insulin resistance through pharmacological interventions, such as metformin, can help mitigate the long-term health risks, especially cardiovascular disease, diabetes, and dyslipidemia, associated with PCOS in aging women [57].

Furthermore, it is crucial to consider the reproductive aspirations of aging women with PCOS. It is well known that PCOS stands as one of the predominant reasons for infertility due to anovulation, affecting up to 80% [58]. Discussing fertility desires and potential barriers early on allows for informed decision-making and appropriate interventions. Collaboration between reproductive endocrinologists and other specialists is essential to provide comprehensive care tailored to the individual needs of aging women with PCOS, including the consideration of fertility preservation options and assisted reproductive techniques [59].

Fertility Preservation Options for Women with PCOS

Infertility is a common consequence of anovulation in PCOS, necessitating interventions to restore ovulatory function and enhance fertility. Fertility preservation options play a vital role in addressing the reproductive concerns of women with PCOS, particularly in the context of aging and declining ovarian reserve.

The management of ovulatory dysfunction and infertility requires a comprehensive approach in PCOS that encompasses both ovulation induction and assisted reproductive techniques (ART). By employing a combination of pharmacological interventions and advanced ART, clinicians can significantly enhance the chances of successful pregnancy in this patient population.

The choice of method for induction of ovulation or other fertility preservation option should be individualized, considering factors such as age, ovarian reserve, and personal preferences. Counseling and shared decision-making with reproductive specialists can guide women with PCOS in making informed choices regarding fertility preservation, taking into account their unique circumstances and reproductive goals. While ovulation induction focuses on restoring natural fertility, ART offers an effective approach for couples facing more complex infertility challenges.

The used methods for induction of ovulation include:
1. Lifestyle Modifications: Lifestyle changes, including weight loss and exercise, play a pivotal role in restoring ovulation and improving fertility in PCOS. Weight loss can reduce insulin resistance, ameliorating hormonal imbalances [60].
2. Clomiphene Citrate (CC): CC is a selective estrogen receptor modulator that enhances follicular growth and ovulation. It is administered orally for several days during the menstrual cycle and until recently was the first line of treatment for ovulation induction [58].
3. Letrozole: An aromatase inhibitor, letrozole, promotes ovulation by inhibiting the conversion of androgens to estrogens, thus enhancing FSH secretion, which induces follicular development and maturation. Today letrozole is the drug of choice for ovulation induction, showing a 40-60% higher pregnancy success rate compared to clomiphene citrate and fewer associated side effects such as multiple pregnancies, hot flashes, etc [61].
4. Gonadotropins: Gonadotropins are exogenous hormones that replicate the actions of FSH and LH, key regulators of follicular growth and ovulation. The administration of gonadotropins stimulates the development of multiple ovarian follicles, each containing an oocyte. Gonadotropin treatment involves careful monitoring to avoid complications such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Monitoring includes transvaginal ultrasound scans and hormone level assessments to track follicular growth and adjust medication dosages as needed. It is particularly a second-line option for PCOS patients who do not respond well to other ovulation induction methods, such as clomiphene citrate or letrozole [62].
5. Metformin: Metformin improves insulin
sensitivity and reduces hyperinsulinemia, which in turn can mitigate hormonal imbalances and support regular ovulation. The reduction of insulin resistance by metformin is thought to restore the normal functioning of the hypothalamic-pituitary-ovarian axis, ultimately leading to improved follicular development and ovulation. The combined use of metformin and clomiphene citrate capitalizes on their complementary mechanisms of action. Metformin addresses the underlying insulin resistance, which can help potentiate the response to clomiphene citrate and improve its effectiveness in inducing ovulation. The synergy between these medications not only enhances ovulation rates but also increases the chances of achieving a viable pregnancy [61].

Assisted Reproductive Techniques for PCOS and Advanced Maternal Age

Assisted reproductive techniques (ART) play a crucial role in helping women with PCOS and advanced maternal age achieve pregnancy. In Vitro Fertilization (IVF) is a cornerstone of ART, offering a comprehensive solution for PCOS-related infertility [59]. IVF involves controlled ovarian stimulation using gonadotropins to induce the growth of multiple follicles. These follicles are then retrieved and fertilized with sperm in a laboratory setting, leading to the development of embryos. The most viable embryos are subsequently transferred into the uterus, increasing the chances of successful implantation and pregnancy. In women with PCOS, the ovarian response to ovarian stimulation for IVF may be exaggerated due to the higher number of follicles present. Therefore, careful monitoring and adjustment of the stimulation protocol are essential to prevent complications such as OHSS. Additionally, personalized approaches to ovarian stimulation include the use of antagonist protocols [63].

Intracytoplasmic Sperm Injection (ICSI) is often integrated into IVF protocols for PCOS patients with associated male factor infertility. This technique involves directly injecting a single sperm into an egg to facilitate fertilization. ICSI ensures that even in cases of reduced sperm quality, the fertilization process can be successfully achieved, enhancing the likelihood of pregnancy [62].

Preimplantation Genetic Testing (PGT) is an advanced technique employed during IVF to screen embryos for chromosomal abnormalities before transfer. Given that PCOS patients may have an increased risk of miscarriage, PGT can identify embryos with normal chromosomal content, consequently reducing the risk of implantation failure and miscarriage [64].

Frozen Embryo Transfer (FET) is an integral component of ART, allowing embryos to be cryopreserved and stored for future use. This technique is particularly beneficial for PCOS patients and aging women as it provides an opportunity for precise timing of embryo transfer during a natural or medicated cycle, optimizing endometrial receptivity [65].

Potential Interventions and Therapeutic Strategies

Lifestyle Modifications: Diet, Exercise, and Weight Management

Lifestyle modifications, including diet, exercise, and weight management is essential in the management of PCOS, aging, and fertility. Adopting a balanced and nutritious diet, rich in fruits, vegetables, whole grains, and lean proteins, can help regulate insulin levels, improve metabolic health, and support reproductive function. Regular physical activity and exercise have been shown to enhance insulin sensitivity, promote weight loss, and improve ovulatory function in women with PCOS. Additionally, achieving and maintaining a healthy weight through lifestyle modifications can positively impact hormone levels, menstrual regularity, and fertility outcomes in women with PCOS and aging women.

Pharmacological Interventions and Hormonal Therapies

Pharmacological interventions and hormonal therapies are commonly employed to manage the symptoms of PCOS, mitigate age-related changes, and enhance fertility outcomes. Metformin and other insulin-sensitizing medication are often prescribed to improve insulin resistance, regulate menstrual cycles, and enhance ovulatory function in women with PCOS. Hormonal therapies, such as oral contraceptives and anti-androgens, may be used to manage hyperandrogenism and regulate menstrual cycles in women with PCOS. Additionally, in certain cases, ovulation induction medications, such as clomiphene citrate or letrozole, can be utilized to stimulate ovulation and improve fertility outcomes. These pharmacological interventions and hormonal therapies should be tailored to individual needs, considering factors such as age, reproductive goals, and comorbidities.

Emerging Technologies and Innovations

Emerging technologies and innovations hold promise in the field of PCOS, aging, and fertility. Advancements in assisted reproductive techniques, such as the use of PGT to select chromosomally normal embryos, can improve the success rates of fertility treatments in women with PCOS and advanced maternal age. Additionally, techniques like ovarian tissue cryopreservation
and in vitro maturation (IVM) of oocytes offer alternative options for fertility preservation and treatment, particularly for women with PCOS [66]. Furthermore, advancements in the field of reproductive genetics and personalized medicine may provide opportunities for targeted interventions and precision treatments based on an individual’s genetic profile.

Future Directions and Promising Research Areas

Future research in PCOS, aging, and fertility holds several promising areas of investigation. Understanding the underlying mechanisms linking PCOS, aging, and fertility can help identify novel therapeutic targets and interventions. Research exploring the role of epigenetics, mitochondrial function, and cellular aging in PCOS and age-related changes in fertility may provide valuable insights into potential interventions. Furthermore, investigating the impact of environmental factors, lifestyle factors, and the gut microbiome on PCOS and age-related fertility decline can contribute to personalized approaches and preventive strategies. Additionally, studies focusing on optimizing the use of existing therapies, developing novel drugs, and exploring regenerative medicine approaches may pave the way for improved outcomes in women with PCOS and aging women seeking to conceive.

By advancing research in these areas and translating findings into clinical practice, we can enhance our understanding of PCOS, aging, and fertility, and develop effective interventions and therapeutic strategies that improve reproductive outcomes and overall well-being in affected individuals.

Implications for Clinical Practice and Research

Clinicians should be aware of the unique challenges in diagnosing and managing PCOS in aging women, taking into account age-related variations in hormonal levels and ovarian function. Lifestyle modifications, including diet, exercise, and weight management, should be emphasized as crucial components of PCOS management in order to improve metabolic health and optimize fertility outcomes. Pharmacological interventions and hormonal therapies can be tailored to individual needs to address specific symptoms and enhance reproductive function. Fertility preservation options, such as oocyte cryopreservation and ovarian tissue cryopreservation, provide valuable opportunities for women with PCOS to preserve their fertility potential.

In terms of research, further investigation into the shared mechanisms underlying PCOS, aging, and fertility is warranted. Understanding the genetic and epigenetic influences, as well as the impact of environmental factors, on these conditions can guide the development of personalized interventions and preventive strategies. Additionally, advancements in assisted reproductive techniques, emerging technologies, and innovations offer exciting avenues for improving fertility outcomes in women with PCOS and aging women.

Conclusion

This narrative review has explored the intricate dynamics of PCOS, aging, and fertility, shedding light on their overlapping mechanisms, potential interventions, and therapeutic strategies. Key findings include the shared hormonal dysregulation, insulin resistance, inflammation, and oxidative stress observed in both PCOS and aging women, which contribute to ovulatory dysfunction, impaired folliculogenesis, and suboptimal fertility outcomes. Additionally, genetic and epigenetic influences have been identified as important factors in developing and progressing PCOS and age-related changes in reproductive function. The review also discussed the diagnosis and management of PCOS in aging women, fertility preservation options for women with PCOS, and the role of assisted reproductive techniques in enhancing fertility outcomes.

In conclusion, this narrative review has provided valuable insights into the complex interplay between PCOS, aging, and fertility. By unraveling the underlying mechanisms, exploring potential interventions, and emphasizing personalized approaches, healthcare professionals can enhance reproductive outcomes and overall well-being in women affected by PCOS as they age. Further research in this field will continue to advance our understanding and contribute to improved clinical practice, ultimately benefiting individuals seeking to optimize their fertility potential and reproductive health.

DISCLAIMER
No part of this article was copied or published elsewhere in whole or in part.

ACKNOWLEDGMENTS
None.

FUNDING
No funding was received for this article.


