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# Latest advancement in reproductive Technologies and their impact on fertility outcomes in women with polycystic ovary syndrome.

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**Abstract**
Polycystic ovary syndrome (PCOS) presents a significant challenge in managing infertility due to its complex pathophysiology. Recent advancements in reproductive technologies offer promising avenues to improve fertility outcomes in women with PCOS. This review explores the latest advancements and their impact on fertility outcomes in this population. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have emerged as key treatments for PCOS-related infertility. These techniques enable precise control over ovulation induction and gamete manipulation, addressing the irregularities in ovarian function characteristic of PCOS. Moreover, the use of gonadotropin-releasing hormone (GnRH) agonists for oocyte triggering has shown efficacy in reducing the risk of ovarian hyperstimulation syndrome (OHSS) in PCOS patients undergoing IVF.
Additionally, lifestyle interventions focused on weight management have gained prominence as a cornerstone of PCOS management, with studies demonstrating the beneficial effects of weight loss on restoring menstrual regularity and spontaneous ovulation. Pharmacological agents such as metformin, liraglutide, and aromatase inhibitors offer alternative options for ovulation induction in cases resistant to conventional treatments like clomiphene citrate.
Overall, the integration of these advancements in assisted reproductive technologies (ART) and individualized treatment approaches holds promise for optimizing fertility outcomes in women with PCOS. However, further research is warranted to refine treatment protocols, enhance success rates, and minimize potential risks associated with these interventions.
**Keywords:** *Infertility, Metformin, Ovulation induction, Polycystic ovary syndrome, Reproductive techniques.*

## Introduction

**Polycystic ovary syndrome (PCOS)** is widely acknowledged as the predominant endocrine disorder in reproductive-age women, with prevalence estimates ranging from 6% to 15%, depending on the diagnostic criteria used [1, 2]. PCOS is marked by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. The 2003 Rotterdam criteria, established jointly by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, serve as the globally accepted diagnostic criteria for PCOS [3, 4]. PCOS is a complex condition characterized by a variety of phenotypes, posing unique challenges in both patient care and medical research. Diagnosis of PCOS requires the fulfillment of two out of three criteria: irregular ovulation or lack of ovulation, clinical and/or biochemical indications of hyperandrogenism, and/or the presence of polycystic ovaries (PCO), along with the exclusion of other potential causes such as congenital adrenal hyperplasia and androgen-secreting tumors [2, 4].

Mounting evidence suggests an increased occurrence of pregnancy complications in women with PCOS. Previous studies have shown a link between PCOS and adverse pregnancy outcomes. The multifactorial pathophysiology of PCOS involves a genetic predisposition exacerbated by excess adiposity. The interaction between abnormal ovarian morphology, heightened androgen production, hyperinsulinemia, and elevated luteinizing hormone (LH) levels contributes to the condition [5, 6]. PCOS can manifest with varying signs and symptoms, indicating different levels of hyperandrogenemia. This has significant implications for a woman's reproductive health and the long-term well-being of her offspring. Developing interventions for women of childbearing age could help reduce adverse neonatal outcomes associated with PCOS [7]. Addressing subfertility linked to PCOS commonly involves a multifaceted approach, encompassing lifestyle adjustments, pharmacotherapy, surgical interventions, and assisted reproductive technologies (ART). Additionally, recent

advancements have introduced alternative and adjunctive treatments, prompting considerations for modifications to the treatment protocol [8, 9].

This narrative review aims to analyze recent advancements in reproductive technologies and their impact on fertility outcomes in women with polycystic ovary syndrome (PCOS). The objective is to assess the correlation between PCOS and adverse pregnancy-related outcomes in assisted reproduction, providing insights for preventive measures and public health interventions.

**Overview of Polycystic Ovary Syndrome (PCOS) and its Impact on Fertility.**

Polycystic ovary syndrome (PCOS) stands as the leading cause of anovulatory infertility, with approximately 90-95% of women seeking infertility treatment affected by it [10]. Many women may discover they have PCOS only upon seeking infertility assistance [11]. PCOS typically involves elevated levels of luteinizing hormone and reduced levels of follicle-stimulating hormone (FSH), alongside increased levels of androgens and insulin. These hormonal imbalances often lead to irregular menstrual cycles, characterized by oligomenorrhea or amenorrhea (infrequent or absent menstruation). Additionally, PCOS can manifest in various clinical features, such as small cysts on the ovaries' surface and symptoms related to excess hair growth and skin issues [12]. Pregnant women with PCOS face a higher risk of developing gestational diabetes mellitus and experiencing first-trimester spontaneous abortions compared to those without PCOS.

**Assisted Reproductive Technologies (ART) for Women with PCOS.**

Assisted reproductive technologies (ARTs) encompass various procedures aimed at facilitating the interaction between sperm and eggs to increase the likelihood of fertilization and achieve successful conception. ARTs include techniques such as intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI), each involving multiple sequential steps to optimize outcomes [13,14].

Before proceeding with ART procedures, it is essential to pharmacologically stimulate the ovaries to produce an adequate number of eggs and prepare the semen sample in the laboratory to obtain motile and morphologically normal sperm. Each procedure is performed based on specific indications. For instance, ICSI is typically used for cases with severe impairment of semen quality, while IUI is suitable for mild-to-moderate impairment in semen quality and other factors such as cervical hostility, endometriosis, and unexplained infertility. The success rate for IUI ranges from 15% to 20% [15-18].

In IVF, both sperm and eggs are cultured in the laboratory to fertilize eggs, making it suitable for indications such as female tubal obstruction and severe endometriosis, as well as those for IUI. ICSI, introduced in 1990, is considered the preferred ART option for severe male factor infertility treatment [19]. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are advanced reproductive technologies used for treating infertility, with IVF being suitable for indications like female tubal obstruction and severe endometriosis. ICSI, introduced in 1990, is considered the gold standard for severe male factor infertility treatment, offering high success rates. However, both IVF and ICSI are associated with complications such as ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. For women with polycystic ovary syndrome (PCOS), restoring normal ovulation is a primary treatment goal. Pharmacological agents targeting insulin resistance can improve ovulation rates. Despite this, PCOS patients still face a higher risk of fetal loss. ARTs like IVF and ICSI are viable options for PCOS patients who do not respond to conventional treatments. ICSI can overcome

fertilization issues associated with PCOS by directly injecting sperm into the egg, potentially improving fertilization rates and embryo quality. Additionally, ARTs allow for the selection of top-quality embryos, reducing the risk of multiple pregnancies. Therefore, ICSI may offer better biological outcomes for PCOS patients.

**In vitro Fertilization (IVF) and PCOS: Current Practices and Success Rates.**

In vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) is suggested as a third-line treatment option or when other infertility factors are present (clinical consensus conditional recommendation). A meta-analysis conducted by Heijnen et al. revealed comparable pregnancy or live birth rates per initiated IVF cycle among women with and without PCOS [20].

In vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) is suggested as a third-line treatment option or when other infertility factors are present (clinical consensus conditional recommendation). A meta-analysis conducted by Heijnen et al. revealed comparable pregnancy or live birth rates per initiated IVF cycle among women with and without PCOS [21].

The use of GnRH agonist instead of hCG for oocyte triggering has shown effectiveness in reducing ovarian hyperstimulation syndrome (OHSS). To mitigate the negative impact on pregnancy outcomes in autologous cycles, this approach can be followed by a "freeze-all" program, where embryo transfer is not carried out in the fresh autologous cycle. Instead, frozen embryo transfer is performed in a subsequent cycle. The freeze-all strategy proves advantageous for improving pregnancy outcomes, particularly in high responders with 15 or more oocytes retrieved [22,23].

The initial stage of IVF±ICSI involves ovarian hyperstimulation to stimulate the development of multiple follicles. Typically, this protocol includes the simultaneous administration of GnRH analogues and gonadotropins. In women with PCOS undergoing IVF±ICSI, studies have found no significant difference between the use of urinary or recombinant follicle stimulation hormone, and there appears to be no advantage in supplementing with exogenous LH [24,25].

**Ovulation Induction Techniques in PCOS Management**

Since 70% of women with PCOS experience anovulation or oligoovulation, inducing ovulation is the primary focus for treating infertility in this population.For women with PCOS and infertility attributed solely to anovulation, with normal semen analysis, tubal patency testing such as hysterosalpingography or hysterosonosalpingography should be considered before initiating ovulation induction, especially when tubal infertility is suspected. Tubal abnormalities contribute to infertility in approximately 20% of subfertile couples. The WHO's evidence report on infertility treatment in PCOS underscores the importance of assessing tubal patency during infertility evaluations. The most frequently used drugs for ovulation induction: letrozole, clomiphene citrate (CC), and gonadotropins are further explained.

**Table 1: Ovulation Induction (OI) techniques.** [26]

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| Weight loss and lifestyle modifications | – | – | Loss around 5–10% of body weight [27,28] | – | – | •Reduce hyperinsulinemia, [27–31] • Increase insulin sensitivity, |

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| | | | | | | [29,30] • Restore ovulatory cycles, [29,30] • Improve reproductive outcomes including ovulation and menstrual cycle regulation [31]. |
| Myo–Inositol | – | – | – | – | – | • Improving insulin sensitivity [32] • Increasing Sex Hormone Binding Globulin (SHBG) [32] • Decrease free Testosterone [32] • minimizing hyperandrogenic features [32]. • Increase ovulation rates when compared with placebo or no treatment [32] |
| Clomiphene | – | Day 2–5 | 50 mg OD for 5 days–traditional | Progestin prescribed for | Serum progesterone levels, > 3 | • Successful in 70–80% of women [33, 34] • Cumulative |

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| | | | | lack of ovulation and cycle restart Increase by 50 mg for each cycle thereafter until response–Upper limit at 250 mg. | ng/mL between days 22 and 25 indicates successful ovulation | pregnancy rates of 70–75% are expected over 6–9 cycles of treatment [35,36] |
| | – | | 50 mg OD for 5 days–"stair step" | Increase by 50 mg if lack of dominant follicle on ultrasound | Ultrasound sonography day 11–14, Repeat ultrasound 1 week after dose increase | • Significantly higher ovulation rates of 64% at 100 mg when compared to the traditional 22% at the same dose [37]<br>• Shorter time to ovulation by 32–53 days when compared to the traditional method [37] |
| | Glucocorticoids | Day 5 | Clomiphene 200 mg OD for 5 days Dexametha | Clomiphene resistant women– | Ultrasound sonograp | • 88% of women had successfully ovulated vs. |

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| | | | sone 2mg OD for 10 days | no progression | hy day 16 or 17 | 20% of in the control group [38] • Cumulative pregnancy rate 40.5% vs. 4.2% in the control group [38] |
| | Metformin | Day 3 | Clomiphene 50 mg OD for 5 days Metformin 500 mg OD– gradually increase to 2g (1g BD) | Increase Clomiphene dose either after 5 weeks of anovulation or after a menses– Upper limit at 150 mg | If 2 consecutive serum progesterone levels > 5ng/mL then weekly pregnancy test until positive or menses occurred | • Clomiphene alone and Clomiphene with Metformin is superior to Metformin alone in live birth rate [39] • Comparable live birth rate in Clomiphene vs. Clomiphene with Metformin [39] |
| | Myo–Inositol | No available evidence/protocol in the literature for comparison with other protocols | | | | |
| Letrozole | – | Day 3–5 | 2.5 mg OD for 5 days | Increase by 2.5 mg for each cycle thereafter until response–Upper limit at 7.5 mg Max 5 | Mid luteal progesterone >3 ng/mL | • Higher cumulative pregnancy rate (27.3% vs. 21.5%) and higher live birth (27.5% vs. 19.1%)[40] when compared to Clomiphene |

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| | | | | cycles for each patient | | • Higher proportion of women achieve ovulation (88.5% vs. 76.6%), and a higher proportion of ovulations over total treatment (61.7% vs. 48.3%) when compared to Clomiphene [40] |
| Exogenous Gonadotropins | – | Day 3–5 | 75IU hMG/rFSH OD for 5 days–conventional protocol | Increase by 75IU hMG/rFSH until response Triggered with 5,000–10,000 IU hCG | Elevated levels of Estradiol when compared to background Ultrasound sonography for Follicular visualization and triggering | • Cumulative conception rates of around 90% and cumulative live birth rates of 85% after 12 cycles (41)<br>• Risk for OHSS and multifetal pregnancy (42,43) |
| | – | | 37.5–75IU hMG/rFSH OD for 8–14 days–chronic low dose | Increase by 37.5–75IU hMG/rFSH until response Triggered with | | • Similar cumulative pregnancy and live birth rate with conventional protocol (44,45)<br>• Smaller |

| Intervention | Supplementary drug | OI Initiation (Day of Cycle) | Protocol | Protocol progression | Protocol monitoring | Expected result |
|---|---|---|---|---|---|---|
| | | | | 5,000–10,000 IU hCG | | OHSS and multifetal pregnancy risk than conventional protocol (44,45) |
| Laparoscopic Ovarian Drilling | – | – | – | Often reserved for medication resistant women– No progression | – | • Similar in live birth rates compared to clomiphene citrate and metformin, gonadotrophins (46).<br>• Lower live birth rates when compared to letrozole [46]. |

**Emerging Technologies and Innovations in PCOS Treatment**

The treatment approach for PCOS should aim not only to alleviate symptoms but also to prevent long-term complications. Standard care often involves the use of combined oral contraceptives and antiandrogens to lower androgen levels, manage symptoms, and offer endometrial protection.[47] However, treatment plans should be individualized based on the patient's desire for pregnancy, aesthetic concerns, and the presence of concurrent metabolic issues.[48]

The overarching objectives of therapy for women with PCOS include addressing hyperandrogenic symptoms, managing metabolic abnormalities, reducing the risk factors for

conditions like type 2 diabetes and cardiovascular disease, preventing endometrial hyperplasia, facilitating safe pregnancy if desired, and enhancing overall well-being and quality of life. Achieving these goals typically requires a multidisciplinary approach focused on providing patient-centered care.[49]


**Figure 1:** Patient-centered care by a multidisciplinary team may help reach the main goals of polycystic ovary syndrome management. Ref [50]

**Metabolism**

The primary approach to treating patients with PCOS should focus on lifestyle modifications. In overweight and obese individuals, changes in diet and physical activity leading to weight loss can help reduce serum insulin and androgen levels, lowering the risk of glucose intolerance and type 2 diabetes. Pharmacological interventions become necessary if insulin resistance (IR)/glucose intolerance or dyslipidemia persist despite lifestyle modifications.[51]

Metformin is commonly prescribed for metabolic control in PCOS patients due to its insulin-sensitizing and hypoglycemic effects, which have been well-documented.[52] However, while metformin may not significantly reduce BMI compared to placebo, it can offer minimal benefits in combination with antiandrogen therapy or combined oral contraceptives. Metformin's impact on reducing body adiposity, waist circumference, and serum triglyceride levels in women with PCOS appears limited. Ongoing research is exploring genetic variations to determine individual responsiveness to metformin therapy. Additionally, novel pharmaceutical formulations designed for vaginal delivery are being developed to mitigate metformin's gastrointestinal side effects, showing promise in preclinical PCOS models.[53]

Liraglutide, a glucagon-like peptide receptor 1 agonist, has been approved for treating type 2 diabetes and obesity. In obese women with PCOS, liraglutide has demonstrated effectiveness in inducing significant weight loss and reducing waist circumference. Orlistat, a lipase inhibitor indicated for obesity treatment, has shown efficacy in inducing weight loss and improving hyperandrogenism and IR markers in overweight or obese women with PCOS.[54]

Myo- and D-chiro-inositol, insulin-sensitizing agents acting as second messengers in insulin signaling, have been investigated as alternatives to metformin in PCOS women with IR. These compounds influence insulin activity in various target organs, including the ovary. Clinical studies have shown reductions in serum testosterone levels and increases in SHBG levels after myo-inositol treatment, with no significant difference in mature oocyte retrieval for IVF between D-chiro-inositol alone or combined with myo-inositol. However, recent meta-analyses suggest that myo-inositol supplementation for IVF may not enhance oocyte or embryo quality.[55]

While inositol therapy may emerge as an alternative for metabolic improvement in PCOS patients intolerant to metformin, robust comparative data with metformin are still lacking.

Several small randomized controlled studies have yielded conflicting results regarding the efficacy of inositols versus metformin, warranting further investigation. The International PCOS Network considers inositol therapy as experimental in PCOS management.[56]

**Quality of life**

PCOS typically affects women during their reproductive years, a time when concerns about relationships, intimacy, and starting a family are prominent. Physical changes that impact appearance or fertility can provoke significant anxiety and disrupt the psychosexual aspect of life. Research indicates that the psychological toll of PCOS may exceed that of chronic conditions like asthma, diabetes, arthritis, and coronary heart disease.

Depression and anxiety are prevalent among women with PCOS. Studies have shown a significant increase in depressive symptoms among individuals with the syndrome compared to controls, even after adjusting for BMI. Common symptoms include daily fatigue, sleep disturbances, appetite changes, and loss of interest in usual activities. Therefore, assessing the quality of life in women with PCOS is crucial for effective care and clinical management of these patients. [57]

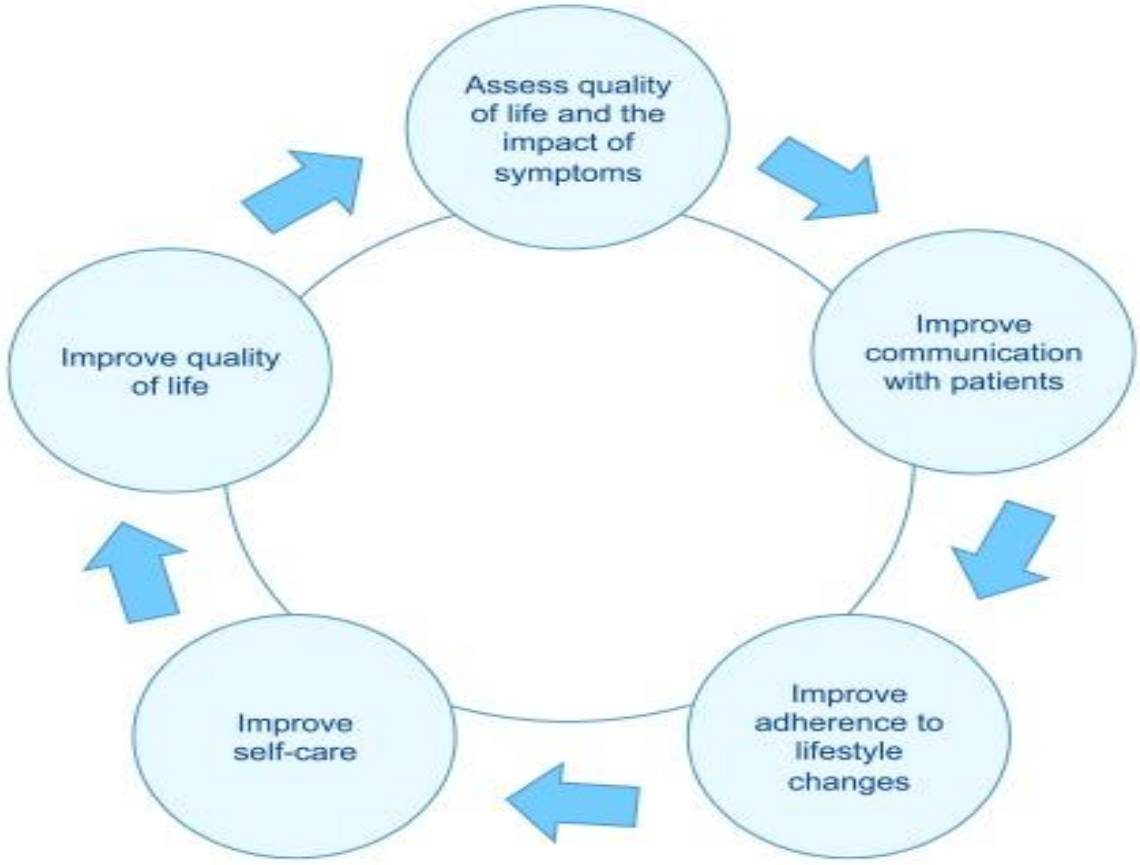


**Figure 2:** Objectives of assessing the quality of life in women with polycystic ovary syndrome. Ref [50]

**Infertility**

In overweight or obese patients with PCOS aiming to conceive, lifestyle adjustments focusing on weight loss should be the cornerstone of preconception counseling. Shedding 5 to 7% of body weight can help regulate menstrual cycles and promote spontaneous ovulation. If weight loss is challenging or fails to restore ovulatory cycles, treatment should be personalized, considering factors such as infertility duration, age, pregnancy risks, and barriers to weight loss. Preconception care should also include folic acid supplementation (0.4 mg/day) and cessation of smoking and alcohol consumption.

Ovulation induction becomes the second-line treatment following lifestyle modifications. Prior to initiating this step, other causes of infertility like male factor or tubal obstruction, which may require IVF, should be carefully evaluated.

Clomiphene citrate (CC) is the standard therapy for inducing ovulation in anovulatory women with PCOS. If ovulation does not occur after three cycles of maximum-dose CC (150 mg/day), the woman may be considered non-responsive, and an alternative drug should be considered.

Metformin has shown to reduce testosterone levels, increase spontaneous ovulation, and promote regular menstrual cycles in PCOS patients. [58] However, it is no longer recommended as first-line ovulation induction due to lower live birth rates compared to CC. The combination of metformin with CC may increase ovulation and clinical pregnancy rates but also the risk of miscarriage. In metformin-resistant cases, adding metformin may enhance the pregnancy rate. However, maintaining metformin during pregnancy does not appear to prevent adverse outcomes and may increase the risk of future offspring overweight.[59]

Letrozole, an aromatase inhibitor, can serve as an alternative to induce ovulation in patients unresponsive to CC. It has shown superior ovulation-inducing response, especially in obese patients, leading to higher pregnancy and live birth rates compared to CC. Letrozole may also outperform metformin plus CC in inducing ovulation, as suggested by preliminary data.

If oral ovulation inducers fail, injectable gonadotropins combined with timed intercourse, intrauterine insemination, or IVF may be considered. Adding metformin to gonadotropins has demonstrated some benefit in low-complexity treatments but not in IVF. Preliminary findings suggest that low-dose liraglutide may improve IVF outcomes in obese women with PCOS.

Women with PCOS should receive counseling on the optimal timing for pregnancy, considering obstetric, metabolic, and cardiovascular risks. Safe contraception is integral to

comprehensive care, allowing time for lifestyle interventions to improve metabolic health and facilitate successful full-term pregnancies for both mother and baby.[60]

**Challenges and Limitations in Reproductive Technologies for PCOS.**

Polycystic ovary syndrome (PCOS) presents unique challenges and limitations in the realm of reproductive technologies due to its complex pathophysiology and multifaceted clinical manifestations. Here are some key challenges and limitations:

**Ovulation Induction:** One of the primary challenges in PCOS management is inducing ovulation, particularly in patients who are resistant to standard ovulation induction medications such as clomiphene citrate (CC). While CC is the first-line therapy, a significant proportion of PCOS patients do not respond adequately to this treatment. Alternative medications like letrozole have shown promise but may still have limitations in certain patient populations.

**Hyperstimulation Risk:** Ovarian hyperstimulation syndrome (OHSS) is a potential complication of assisted reproductive technologies (ART) in PCOS patients. Due to their hyperresponsive ovaries, PCOS patients are at increased risk of developing severe OHSS, which can lead to serious complications and compromise treatment outcomes.

**Increased Miscarriage Risk**: PCOS patients undergoing ART may face a higher risk of miscarriage compared to women without PCOS. This increased risk may be attributable to various factors, including hormonal imbalances, insulin resistance, and metabolic dysfunction associated with PCOS.

**Metabolic Factors:** Metabolic abnormalities such as insulin resistance, obesity, and dyslipidemia commonly coexist with PCOS and can impact the success of reproductive technologies. These metabolic factors may influence ovarian response to stimulation, embryo quality, implantation rates, and pregnancy outcomes.

**Individualized Treatment:** PCOS is a heterogeneous condition with diverse clinical presentations and underlying pathophysiologies. Tailoring treatment approaches to individual patient profiles and addressing specific metabolic and reproductive concerns can be challenging but essential for optimizing outcomes.

**Long-term Health Considerations:** While reproductive technologies offer opportunities for achieving pregnancy in PCOS patients, long-term health considerations must be taken into account. PCOS is associated with an increased risk of metabolic disorders, cardiovascular disease, and other health complications, which may influence decisions regarding fertility treatment.

**Psychological Impact:** The psychological burden of infertility and its treatment can be particularly significant for women with PCOS. Managing the emotional stress, anxiety, and depression associated with infertility challenges is an important aspect of holistic care for PCOS patients undergoing reproductive technologies.

Addressing these challenges and limitations requires a comprehensive and multidisciplinary approach that integrates medical, reproductive, psychological, and lifestyle interventions tailored to the individual needs of PCOS patients. Close collaboration between fertility specialists, endocrinologists, mental health professionals, and other healthcare providers is essential for optimizing outcomes and supporting the overall well-being of individuals with PCOS seeking fertility treatment.

**Future Directions and Potential Advances in PCOS Management.**

Future directions in PCOS management may include personalized treatment approaches targeting specific phenotypic and metabolic characteristics, advancements in ovulation induction strategies with a focus on minimizing complications such as OHSS, integration of

digital health technologies for remote monitoring and support, and further research into the underlying pathophysiology of PCOS to identify novel therapeutic targets and interventions.

**Conclusion.**

In conclusion, advancements in reproductive technologies offer promising prospects for improving fertility outcomes in women with PCOS. Tailored treatment approaches addressing individual phenotypic and metabolic characteristics, along with the integration of innovative ovulation induction strategies, hold potential to enhance success rates while minimizing risks. Additionally, leveraging digital health technologies for remote monitoring and support can further optimize patient care. Continued research into the underlying mechanisms of PCOS and the development of targeted interventions will be crucial for optimizing fertility outcomes and ensuring the well-being of women with this condition in their journey to conception and successful pregnancy.

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