Exploring Hormone Regulation-Associated Genes as Novel Targets for Gene Therapy in Polycystic Ovary Syndrome (PCOS)

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Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder impacting a significant percentage of women worldwide. Despite its prevalence, the understanding of PCOS remains incomplete, and current treatments primarily focus on symptom management. This review seeks to address specific gaps in our understanding of PCOS by exploring the potential of gene therapy as an innovative treatment approach. The objectives include identifying the genetic factors contributing to PCOS, discussing the challenges in current treatments, and interpreting how gene therapy could address these gaps. By examining successful applications in other genetic disorders, the paper aims to provide insights into the potential contributions of gene therapy in managing PCOS, contributing to the advancement of therapeutic strategies for this complex syndrome.

Introduction

This paper details a compelling exploration of the transformative potential of gene therapy in tackling the intricate challenges posed by Polycystic Ovary Syndrome (PCOS). Discovered in the 18th century by Dr. Antonio Vallisneri, PCOS has remained a pervasive endocrine disorder affecting women, with diverse treatments targeting its multifaceted symptoms. In the 20th century, the advent of gene therapy marked a revolutionary stride in addressing genetic diseases, offering hope for conditions with underlying genetic factors. This paper traces gene therapy's evolution and weaves a narrative that intimately connects it to the complexities of PCOS.

Gene therapy, which involves manipulating genetic material to address the root causes of diseases, has emerged from early setbacks to triumph in treating disorders like Leber's congenital amaurosis (LCA) and severe combined immunodeficiency (SCID). These underscore the transformative potential of gene therapy, positioning it as a beacon of hope in medical innovation (Tamura and Toda, 2020)[1].

However, the full scope of gene therapy's applications has yet to be realized, particularly in PCOS. The syndrome's intricate interplay of genetic and environmental factors presents a unique challenge that requires a different approach. To unlock the potential of gene therapy for PCOS, it is imperative to unravel the genetic basis of the syndrome, providing a solid foundation for targeted interventions. By honing in on genes responsible for hormone dysregulation and ovarian dysfunction, gene therapy emerges as a promising avenue for addressing the core drivers of PCOS.

Navigating the uncharted territory of applying gene therapy to PCOS is not without obstacles. However, aligning genetic insights with therapeutic techniques yields an exciting prospect for new, groundbreaking treatments. This paper envisions a future in which gene therapy, armed with a deep understanding of PCOS and its genetics, is a beacon of innovation in managing this complex condition.

In conclusion, this paper sheds light on the historical context of PCOS and gene therapy and presents a compelling case for their convergence. By examining successful applications and envisioning tailored approaches for PCOS, the paper contributes meaningfully to the ongoing discourse on innovative strategies for managing this complex syndrome. The transformative potential of gene therapy awaits, poised to revolutionize the landscape of PCOS treatment.

Challenges in Managing PCOS

The causes of PCOS are numerous, and the symptoms of PCOS also coincide with other diseases (e.g., diabetes). This can lead to misdiagnosis. PCOS hinders fertility and increases the risk for many other conditions. Because PCOS has high heterogeneity, the cause can not be targeted. While there is ongoing research, many results show different discoveries about PCOS, furthering confusion regarding the condition. Additionally, the range of potential causes of the symptoms of PCOS leads to misdiagnosis. PCOS can significantly affect a person's quality of life due to its physical, emotional, and social implications. Living with a chronic condition that requires long-term symptom management and potential fertility problems can impact daily life, relationships, and overall well-being.

The inherent condition of PCOS currently has no cure, only symptom management. Irregular menstrual cycles are a prevalent symptom of PCOS. This can be treated with hormonal birth

control, oral contraceptives, or hormonal patches that help regulate menstrual cycles and reduce androgen levels. Progestin medications can also be used to induce regular periods. Hirsutism, excess hair growth, often happens in places that don't typically grow much hair. This can be treated with different hair removal methods, such as shaving, waxing, threading, and depilatory creams. Laser hair removal is a more permanent solution that targets hair follicles with laser energy. Anti-androgen medications can also help reduce excessive hair growth by blocking the effects of androgens (Legro, 2017)[2]. Acne is a common symptom due to hormonal imbalances. This can be treated with topical treatments, such as over-the-counter or prescription creams containing benzoyl peroxide, retinoids, or antibiotics that may be used to treat acne. Hormonal therapy, like oral contraceptives or anti-androgen medications, can help control acne by regulating hormone levels (Sadeghi et al., 2022)[3]. Weight management is critical to managing PCOS due to the weight changes that can occur when suffering from this condition. Lifestyle changes like a balanced diet and regular exercise can help control weight and improve insulin sensitivity.

In some cases, weight loss medications or metformin (an insulin-sensitizing drug) may be prescribed to aid in weight management. Infertility is also a significant symptom; fertility medications can be used to treat this, like ovulation-inducing medications, such as clomiphene citrate or letrozole, which can help stimulate egg release. In-vitro fertilization (IVF) and other fertility treatments may be recommended for those who do not respond to other treatments. Insulin resistance and diabetes are additional risks. Lifestyle changes to combat this are weight management, regular exercise, and a balanced diet, which can improve insulin sensitivity. Metformin can be prescribed to help manage insulin resistance and reduce the risk of developing type 2 diabetes (Ndefo et al., 2013)[4].

As the exact root cause of PCOS remains elusive, the focus of treatment revolves around addressing its symptoms. However, there are limited treatment options that comprehensively alleviate all facets of the syndrome, and patients, driven by their fertility aspirations, may be hesitant to pursue particular therapies despite displaying symptoms. The desire for fertility can hinder some women with PCOS from seeking treatment due to emotional burdens, stigma, anxiety, and misinformation about fertility treatments. Fears of disappointment, invasive procedures, financial constraints, and societal pressures to conceive naturally can contribute to delaying medical assistance. Coping mechanisms and uncertainties about treatment outcomes also play a role. Additionally, women may find it inconvenient and inefficient to target them all separately due to the many different symptoms (Ndefo et al., 2013)[4].

Many common conditions mimic PCOS (e.g., obesity). However, the various conditions cannot always be identified as a cause or effect of PCOS (Khadilkar, 2019)[5].

Women with PCOS can experience many emotional and social implications due to the complex nature of the condition and its impact on various aspects of their lives. The uncertainty and lack of knowledge about PCOS can lead to emotional distress and a lack of support for the condition. Some women may struggle to find adequate support from healthcare providers, friends, or family members who may not fully grasp the impact of the state on their lives. Women may also suffer from body image issues due to symptoms like weight gain, acne, and hirsutism, affecting self-esteem and causing women to be overly self-conscious. Fertility concerns can also affect women. Raising awareness about PCOS and its impact on women's lives can foster understanding and empathy from friends, family, and society.

There is a strong link between obesity and PCOS. While not all women with PCOS are overweight, obesity is common in many individuals with the condition. The relationship between obesity and PCOS is complex and bidirectional, meaning one can contribute to the other and vice versa. Some essential links are insulin resistance, hormonal imbalance, and both obesity and PCOS are linked to the development of type 2 diabetes. It's important to note that not all women with PCOS are obese, and not all obese women have PCOS (Rasquin et al., 2022)[6]. However, managing weight and lifestyle changes, such as maintaining a healthy diet and engaging in frequent physical activity, can positively impact PCOS symptoms and overall health. For individuals with PCOS who are overweight or obese, weight management can be an essential part of their treatment plan to improve insulin sensitivity, regulate hormones, and reduce the risk of long-term health complications (Barber and Franks, 2021)[7].

Diabetes and PCOS are often grouped due to the common misdiagnosis of one another and the coinciding symptoms. PCOS and type 2 diabetes involve insulin resistance, in which the body's cells become less sensitive to insulin's actions. Many hormonal imbalances also occur as a result of both. Both diabetes and PCOS are associated with an increased risk of cardiovascular disease (Zhu and Goodarzi, 2022)[8]. Women with PCOS may have additional cardiovascular risk factors due to the combined effects of insulin resistance, hormonal imbalances, and obesity. PCOS may increase the risk of developing insulin resistance and type 2 diabetes. Early diagnosis, lifestyle modifications, and appropriate medical management are essential in addressing the links between PCOS and diabetes and reducing associated health risks. Women with PCOS should work closely with their healthcare providers to monitor their health, manage symptoms, and reduce the risk of long-term complications, including diabetes (Livadas et al., 2022)[9].

Hypothyroidism (underactive thyroid) and PCOS can share similar symptoms, such as irregular menstrual cycles, weight gain, and fatigue. Additionally, thyroid dysfunction can affect hormonal levels, leading to potential confusion with PCOS. Premature ovarian insufficiency (POI) is when the ovaries stop

functioning before age 40, leading to irregular periods and hormone imbalances. The symptoms of POI may resemble those of PCOS, leading to misdiagnosis (Deswal et al., 2020)[10].

Excessive cortisol levels in the body cause Cushing's syndrome and can lead to weight gain, hirsutism, and irregular menstrual cycles, similar to PCOS. High prolactin levels (hyperprolactinemia) can lead to irregular periods and changes in menstrual cycles, which may be mistaken for PCOS. Non-Classic Congenital Adrenal Hyperplasia (NCAH) is a genetic disorder that affects the adrenal glands and can cause androgen excess, leading to symptoms similar to PCOS. Certain ovarian tumors, such as granulosa cell tumors, can produce excess androgens and lead to symptoms that resemble PCOS (Rosenfield and Ehrmann, 2016)[11].

The robust association between PCOS susceptibility variants, as identified in the meta-analysis of genome-wide association (GWAS) data, and the key variables linked to PCOS strongly support the notion that various genetic variations can contribute to PCOS via diverse mechanisms. This genetic component could signify that PCOS is inheritable and that many women could have a genetic predisposition. This means that without altering the genes in some way using gene therapy, there will likely never be an all-encompassing cure for PCOS.

What is Gene Therapy?

Gene therapy involves altering genes within the human genome, has been a longstanding medical aspiration, dating back to the discovery of Deoxyribonucleic acid (DNA). Its primary objective is the enhancement of genes by rectifying mutations or implementing specific modifications to address various diseases. This field predominantly resides within research laboratories and remains experimental, with ongoing trials conducted in the United States, Europe, and Australia. Gene therapy encompasses a wide array of applications, ranging from treating genetic disorders such as cystic fibrosis, hemophilia, muscular dystrophy, and sickle cell anemia to managing acquired illnesses like cancer and viral infections such as AIDS.

A prevalent technique employed in gene therapy is recombinant DNA technology. This method involves incorporating a desired gene into a vector, which can take various forms, including plasmids, nanostructures, or viruses. Viral vectors are commonly favored due to their efficient ability to transport genetic material into cells. However, Table 1 summarizes approved gene therapy protocols, outlining the associated disease, the target, and the vector utilized.

Which Gene Families Impact PCOS

PCOS is commonly characterized by elevated androgen (male hormone) levels, and genetic factors related to ovarian and adrenal steroidogenesis have been investigated in connection with this condition. Several genes have been implicated, including CYP11a, CYP21, CYP17, and CYP19, each playing a role in the synthesis and regulation of steroid hormones. For instance, CYP11a encodes an enzyme essential for converting cholesterol to progesterone, a key step in steroidogenesis. While some studies have linked CYP11a polymorphisms to PCOS, these associations have not been consistently replicated across all research. Similarly, CYP21, responsible for converting 17-hydroxyprogesterone to 11-deoxycortisol, has shown some associations with PCOS-like conditions, especially in cases of hyperandrogenemia, but direct links remain inconclusive. CYP17, involved in converting pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone, has been associated with elevated androgen levels in PCOS patients. Furthermore, CYP19, which plays a role in estrogen formation, exhibits reduced activity in both obese and lean women with PCOS. While these genetic insights shed light on potential contributors to PCOS, the complexity of the condition suggests that further research is needed to establish definitive links between these genes and PCOS development and progression.

Genes influencing steroid hormone effects and gonadotropin action are associated with PCOS, a hormonal disorder. In the context of steroid hormone effects, the Androgen Receptor gene (AR) on the X chromosome plays a crucial role, as mutations or disruptions in this gene can lead to PCOS. The Sex Hormone-Binding Globulin gene (SHBG) on chromosome 17 is significant. SHBG regulates sex hormone levels by binding to androgens, mainly testosterone and estrogens. Lower SHBG concentrations are observed in females with PCOS, often attributed to the inhibitory effect of hyperinsulinemia. Genetic variations in the SHBG gene are associated with PCOS in several studies.

Regarding gonadotropin action and regulation, both LH (Lutein Hormone) and its receptor have been implicated in PCOS. Elevated LH levels and disturbances in LH function are commonly reported in PCOS cases, leading to abnormalities in ovarian function. High LH levels can stimulate excess androgen production. Furthermore, AMH (Anti-Mullerian Hormone) and FSHR (Follicular Stimulating Hormone Receptor) genes are also linked to PCOS. AMH gene variations are associated with PCOS and have been identified as strong predictors of the condition. FSHR mutations can disrupt the balance of hormonal regulation, contributing to PCOS, as observed in some affected individuals, particularly in certain ethnic populations. These genetic factors provide insights into the complex hormonal dysregulation observed in PCOS.

Genes involved in insulin action and secretion have been implicated in developing PCOS. Insulin, a key regulator of blood sugar, also plays a significant role in the production of androgen hormones in the theca cells of the ovaries, contributing to the hormonal imbalances observed in PCOS. Several genes associated with insulin function and regulation have been studied in the context of PCOS.

Disease	Target	Viral Vector Type
Cystic Fibrosis	Recessive Gene Disorder	Adenovirus
Hemophilia	Recessive Gene Disorder	Adeno-associated virus
Muscular Dystrophy	Recessive Gene Disorder	Lentivirus
Sickle Cell Anemia	Recessive Gene Disorder	Beta-globin lentiviral vector
Cancer	Acquired Genetic Disease	Oncolytic viruses
AIDS	Viral Infection	Lentivirus, Adenovirus

Table 1 Examples of Approved Gene Therapy Protocols for Clinical Use (Gonçalves and Paiva, 2017) [12]

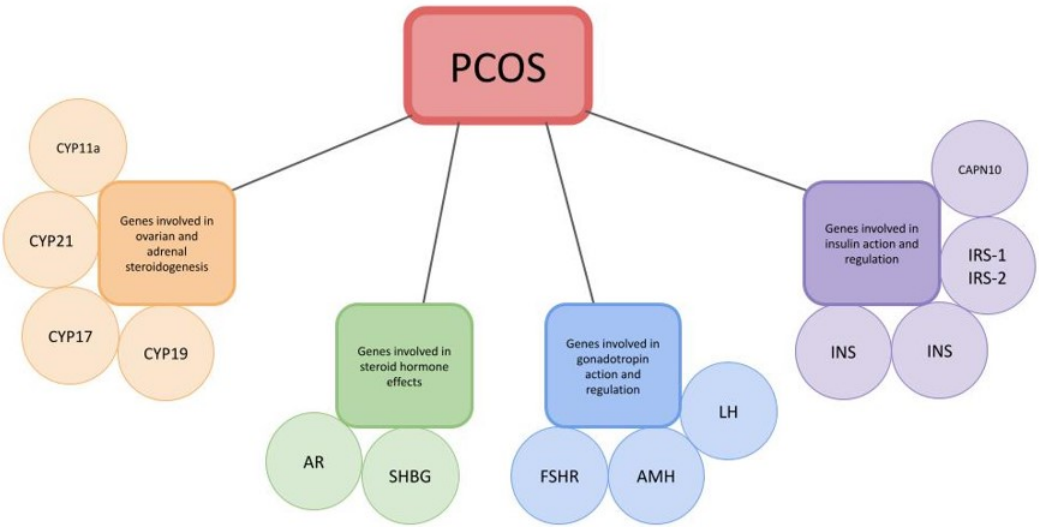

Fig. 1 Primary gene families impacting PCOS (modified from Khan et al., 2019) [13]

The insulin gene (INS) on chromosome 11 has been linked to PCOS through a polymorphism in its variable number tandem repeat (VNTR) region. This genetic variation is associated with alterations in insulin regulation and may contribute to the development of PCOS. However, the association between the insulin receptor gene (INSR) and PCOS remains less clear, with some studies failing to establish a consistent link. Instead, genetic regions encompassing the INS receptor on chromosome 19 have shown stronger associations with PCOS, indicating the disorder's complexity of insulin receptor function. Additionally, insulin receptor substrate proteins (IRS-1 and IRS-2) have been studied for their potential role in PCOS, with mixed findings, possibly influenced by environmental and ethnic factors. The calpain10 gene (CAPN10) on chromosome 2 encodes a protein involved in insulin metabolism and secretion. Mutations in CAPN10 can disrupt insulin function and contribute to PCOS development, making it a candidate gene in PCOS research. These genetic insights underscore the intricate interplay between insulin and PCOS, although the exact genetic mechanisms remain multifaceted and can vary among individuals and populations (Khan et al., 2019) [13].

Investigational New Drugs for PCOS

In the realm of investigational drugs for Polycystic Ovarian Syndrome (PCOS), promising strides have been made, particularly with Gonadotropin-Releasing Hormone (GnRH) antagonists. Despite a Phase II trial showing Elagolix's limited impact on menstrual cycle regulation, it provides valuable insights for future PCOS management. Another avenue of exploration is the neurokinin B receptor antagonist, Fezolinetant (ESN364), showing potential in reducing LH secretion and hyperandrogenism. Sodium-glucose co-transporter type 1 and 2 inhibitors (SGLT1/2is), like Licogliflozin, have also emerged as candidates, demonstrating encouraging results in lowering glucose, insulin, and androgen levels in PCOS patients during a Phase II trial. While these findings offer hope for addressing PCOS complexities, especially when considering the current limitations of gene therapy, further research is crucial to validate results across diverse PCOS populations and understand the long-term impact on clinical outcomes. Overall, investigational drugs present exciting possibilities for personalized PCOS treatments, given the current constraints on exploring gene therapy options (D'Angelo et al., 2023). [14]

Alternative Therapeutic Approaches and Their Comparison to Gene Therapy

While gene therapy holds promise as a potential groundbreaking treatment for PCOS, it is essential to contextualize its outcomes in comparison to existing and emerging therapeutic approaches. The following comparative analysis aims to provide a more comprehensive understanding of the current landscape of PCOS treatments. Firstly, hormonal management with traditional approaches often involving oral contraceptives, progestins, or anti-androgen medications to address symptoms such as irregular menstrual cycles, hirsutism, and acne. Gene therapy, by contrast, aims at addressing the root genetic causes of PCOS, potentially offering a more targeted and fundamental solution to hormonal dysregulation. Next, in traditional approaches, lifestyle modifications, including diet and exercise, play a crucial role in managing PCOS symptoms, especially those related to weight and insulin sensitivity. Gene therapy does not replace the importance of lifestyle interventions but seeks to complement them by targeting the underlying genetic factors contributing to PCOS, potentially enhancing the efficacy of lifestyle changes. Common fertility treatments such as ovulation-inducing medications, in-vitro fertilization (IVF), and other assisted reproductive technologies are common for managing infertility in PCOS. While fertility remains a significant concern for women with PCOS, gene therapy might offer a more holistic approach by addressing both fertility issues and the underlying genetic factors contributing to PCOS. Moreover, current treatments often focus on managing symptoms, providing relief, and improving the quality of life for individuals with PCOS. Gene therapy aims to be more curative by directly targeting the genetic mechanisms responsible for PCOS, potentially offering a long-lasting or even permanent solution. However, established treatments have a longer history of use, providing a wealth of safety data, but may have limitations in addressing the root genetic causes. While promising, gene therapy raises ethical concerns and lacks long-term safety data, emphasizing the need for careful consideration and ongoing research. In summary, gene therapy for PCOS presents a novel approach with the potential for fundamental and targeted intervention. However, it is crucial to recognize that gene therapy is not a standalone solution but should be viewed within the broader context of existing and emerging treatments. Further research, clinical trials, and safety assessments are necessary to position gene therapy as a feasible and effective option for the management of PCOS (Lorenzo et al., 2023)[15].

Concerns and Limitations

Using gene therapy to treat PCOS presents several significant challenges and ethical considerations. PCOS is a complex disorder with various symptoms and underlying causes. Attempting to modify a single gene or gene family associated with PCOS could lead to unforeseen impacts on other related conditions. For instance, editing a gene connected to PCOS might inadvertently worsen conditions like diabetes that often coexist with PCOS. This interconnectedness of genes and conditions makes it difficult to predict the full range of effects before initiating treatment.

Additionally, because of this nuanced approach, the timing for this treatment is not certain. However, early intervention during the genetic predisposition phase, identified through advanced genetic screening, may prevent or mitigate the development of severe symptoms. Furthermore, targeting hormonal dysregulation in the early stages of PCOS could provide long-term benefits, while administering gene therapy during the reproductive age aligns with fertility concerns. Tailoring interventions based on disease progression and symptom severity ensures a personalized approach, and transparent discussions about the potential benefits and risks at different stages empower informed decision-making.

Currently, gene therapy experiments have demonstrated significant progress in treating a range of genetic disorders. This includes inherited diseases like SCID and SMA, employing techniques such as CRISPR-Cas9 for conditions like sickle cell anemia, beta-thalassemia, and cancer treatment through modified immune cells (Belete, 2021)[16]. Promising experiments also extend to eye disorders, hemophilia, neurological diseases, and rare conditions with limited treatment options (Amato et al., 2021)[17]. However, the field's complexity demands rigorous testing and safety assessments before wider implementation. Continuous advancements and ongoing experiments underline gene therapy's potential to revolutionize medicine, but staying updated with current research and reputable sources is advised for the latest developments.

Moreover, gene therapy for PCOS raises ethical concerns. These concerns arise from uncertainties surrounding safety and the long-term consequences of manipulating genes. The lack of accessibility to gene therapy is also troubling, as it could create a scenario where only a privileged few can afford the treatment despite suffering from PCOS. Furthermore, the success of gene therapy might open the door to its misuse for non-therapeutic purposes, such as enhancing specific traits or characteristics rather than solely addressing medical issues.

The complexity of PCOS adds another layer of challenge. Since multiple genes contribute to PCOS, a comprehensive cure would necessitate editing numerous genes. This task might not be practically feasible, both in terms of the technical aspects and the associated costs. Real-world application for individuals with PCOS requires a substantial investment of time and resources to ensure safety and efficacy.

Additionally, the heterogeneous nature of PCOS symptomatology complicates treatment approaches. Two individuals diagnosed with PCOS might exhibit different symptoms and require tailored treatments. This diversity highlights the need for person-

alized and nuanced interventions rather than a one-size-fits-all gene therapy approach.

In conclusion, while gene therapy holds potential for treating PCOS, the intricate genetic landscape, ethical considerations, uncertainties about long-term effects, and the variability of the disorder's presentation all contribute to the complexity of gene therapy as a definitive solution for PCOS treatment.

Clarifications

Our investigation utilizes a systematic review approach to thoroughly assess the current body of literature on gene therapy for PCOS. We opted for this methodology to amalgamate evidence from diverse studies, ensuring a meticulous evaluation of the subject. Acknowledging the potential biases associated with systematic reviews, particularly those related to publication and selection, we undertook measures to minimize these effects. Our approach involved the implementation of an extensive search strategy and stringent inclusion criteria, aiming to enhance the reliability and impartiality of our findings.

The exploration of the literature spanned prominent databases, including PubMed and Web of Science, and searching through works included in Google Scholar searches. We used search terms associated with "gene therapy," "PCOS," and related synonyms to guarantee an all-encompassing survey of the literature. Furthermore, we meticulously examined the reference lists of incorporated studies to pinpoint any supplementary pertinent articles. This comprehensive strategy was adopted to ensure the inclusion of all relevant research on gene therapy for PCOS, bolstering the thoroughness and comprehensiveness of our review.

Additionally, the study's inclusion criteria involved clinical trials and observational studies specifically exploring gene therapy interventions in individuals diagnosed with PCOS. We deliberately excluded studies that either did not report pertinent outcomes or exhibited insufficient methodological rigor. This meticulous selection aimed to guarantee the reliability and relevance of the evidence synthesized in our review, with a preference for more recent and information-rich literature. Nevertheless, it's crucial to recognize that the exclusion of certain studies might constrain the generalizability of our findings to particular populations or interventions.

The analyses throughout the paper provide both quantitative outcomes from the studies included, encompassing measures of hormonal regulation, metabolic parameters, and clinical endpoints like menstrual regularity and ovulation induction. For instance, Khan et al. (2019)[13] extensively elucidated the influence of each gene on various hormones within the body, substantiating their findings with abundant qualitative evidence. Through the provision of such precise data, our objective is to clarify the efficacy and potential advantages of gene therapy in mitigating pivotal manifestations of PCOS.

Within our paper, we underscore the significance of elucidating the sample sizes of the referenced studies or trials, particularly within the diverse landscape of PCOS. It remains crucial to appraise the representativeness of these samples and gauge their statistical significance concerning the depicted research outcomes. The inherent heterogeneity of PCOS, spanning a spectrum of clinical manifestations and underlying etiologies, necessitates careful consideration. Hence, future investigations with expanded and more varied sample sizes are imperative to augment the applicability of findings and deepen our comprehension of the effects of gene therapy interventions across various phenotypes of PCOS.

Is Gene Therapy on PCOS Feasible in the Next Ten Years?

PCOS is a multifactorial disorder with genetic, hormonal, and metabolic components. While some genetic factors contribute to PCOS, its exact genetic basis is not fully understood. Before gene therapy can be developed for PCOS, a thorough understanding of the specific genes and mechanisms involved is required. The condition itself is not thoroughly understood either, so research would also have to be conducted on the condition itself to figure out the ideal way of conducting gene therapies. This would investigate the ideal time for women to undergo this treatment, such as before or after pregnancy and at what age.

The development of gene therapies requires extensive research to identify the precise genetic targets, delivery methods, and potential risks associated with the treatment. Researchers continually advance our understanding of gene therapy techniques, but translating this research into effective treatments can take time. After preclinical research, gene therapies must undergo rigorous clinical trials to assess their safety and efficacy. These trials involve multiple phases and can take years to complete. Gene therapy must successfully pass through these trial phases to become a feasible treatment for PCOS. Additionally, any gene therapy, including one for PCOS, would need regulatory approval from health authorities such as the FDA in the United States or the EMA in Europe. This approval process ensures the therapy is safe and effective before making it available to the public.

Considering the multifaceted nature of PCOS, targeting genes involved in insulin action and secretion, such as the insulin receptor gene (INSR), stands out as a particularly promising avenue for gene therapy development. Insulin dysregulation is a key contributor to the hormonal imbalances and metabolic disturbances observed in PCOS. Precision interventions addressing INSR variations could potentially normalize insulin function, offering a comprehensive approach to managing PCOS symptoms. Focusing on this crucial aspect may pave the way for a more effective and targeted gene therapy, with the potential to address both metabolic and hormonal dysregulations associated

with PCOS. However, further research and clinical validation are essential to confirm the efficacy and safety of such targeted gene therapies. This recommendation can be incorporated into the original paper to emphasize a specific and promising genetic target for PCOS gene therapy.

However, even if gene therapy successfully becomes a treatment option for women suffering from PCOS, gene therapy raises ethical concerns that require careful consideration and regulation, especially when involving germline editing. These ethical considerations could also impact the feasibility and timeline of developing gene therapies for such complex conditions as PCOS.

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