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SIG Newsletter

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POR (Poor Ovarian Response)

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Managing Poor Responders in IVF: Insights from the POSEIDON Classification and Latest Evidence

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Introduction

In vitro fertilization (IVF) can be a complex journey, particularly when patients do not respond as expected to ovarian stimulation. The POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) classification system was introduced to address the heterogeneity of poor ovarian response (POR) and provide a tailored approach to

managing these cases. This article explores the management of "unexpected poor responders" in IVF according to the POSEIDON classification and incorporates the latest evidence and strategies for optimizing outcomes.

Understanding the POSEIDON Classification

The POSEIDON classification system divides patients with POR into four groups based on age, ovarian reserve markers (such as antral follicle count (AFC) and anti-Müllerian hormone (AMH) levels), and previous response to ovarian stimulation:

- **Group 1:** Women under 35 years old with normal ovarian reserve but unexpected poor response.
- **Group 2:** Women 35 years or older with normal ovarian reserve but unexpected poor response.
- **Group 3:** Women under 35 years old with low ovarian reserve.
- **Group 4:** Women 35 years or older with low ovarian reserve.

Management Strategies for Poor Responders

1. Optimizing Ovarian Stimulation Protocols

a. The GnRH antagonist protocol and long GnRH agonist protocol are equally recommended for poor responders (Lambalk et al., 2017; Papamentzelopoulou et al., 2021; Prapas et al., 2013; Sunkara et al., 2014).

b. **Gonadotropin Dosing:** Higher initial doses of gonadotropins may be considered to enhance follicular recruitment.
   - The use of either human menopausal gonadotropin (hMG) or recombinant FSH (rFSH) is equally recommended in poor responders (Drakopoulos et al., 2022; Ye et al., 2012).
   - Midcycle addition of hMG in long agonist cycles is probably recommended for patients hyporesponsive to rFSH (Berker et al., 2021; De Placido et al., 2001; Ferraretti et al., 2004; Toporcerová et al., 2005; Wu et al., 2021; Yenigul et al., 2021).
   - Increasing the dose of gonadotropins beyond standard dose (300 IU) to improve live birth rates (LBR) among expected poor ovarian responders is not recommended (Leijdekkers et al., 2019; Lensen et al., 2018; X. Liu et al., 2022, 2023; van Tilborg et al., 2017).

c. **Use of Recombinant LH:**
   - Incorporating recombinant luteinizing hormone (rLH) into the stimulation protocol may benefit some patients, especially those with a relative deficiency in endogenous LH.
   - Recombinant human luteinizing hormone (r-hLH) + rFSH is recommended over rFSH monotherapy in poor responders (Alviggi, Conforti, Esteves, et al., 2018; Conforti et al., 2019; Humaidan et al., 2017; Lehert et al., 2014; Mochtar et al., 2017).
   - Early or midcycle initiation of r-hLH is equally recommended in poor responders (Behre et al., 2015; Revelli et al., 2012).

d. **Dual Stimulation (DuoStim):**
   - This involves two rounds of ovarian stimulation within the same menstrual cycle, aiming to maximize the number of retrieved oocytes in a shorter time frame.
   - The DuoStim protocol is not recommended over the GnRH antagonist protocol in poor responders, as per the IFS POR Guidelines (Kuang et al., 2014; Massin et al., 2023; Sfakianoudis et al., 2020; Ubaldi et al., 2016; Vaiarelli et al., 2020).

2. Adjunctive Treatments

a. Androgen Supplementation:

- Pre-treatment with androgens like DHEA (dehydroepiandrosterone) or testosterone may improve ovarian response by increasing the number of antral follicles and enhancing follicular sensitivity to FSH.
- Dosage and schedule used in literature is, DHEAS 75 mg once a day for 3-6 months.
- As per IFS POR Guidelines, Adjuvant use of dehydroepiandrosterone (DHEA) in ovarian stimulation is not recommended for poor responders (Nagels et al., 2015; J. Zhang et al., 2023). Adjuvant use of testosterone in ovarian stimulation is not recommended for poor responders (González-Comadran et al., 2012; Hoang et al., 2021; Katsika et al., 2023; Nagels et al., 2015; Noventa et al., 2019).

b. Growth Hormone (GH) Supplementation:

- Growth hormone co-treatment has shown potential in improving oocyte quality and ovarian response in some poor responders.
- Dosage of GH as used in literature is 4 IU daily or alternate day along with Gonadotropins from day 2 onwards in the GnRH antagonist cycle and from day 21 onwards in GnRH agonist cycles.
- As per IFS POR Guidelines, adjuvant use of growth hormone (GH) in ovarian stimulation is not recommended for poor responders (Elkalyoubi et al., 2023; Sood et al., 2021).

c. Coenzyme Q10 Supplementation:

- Coenzyme Q10, an antioxidant, has been studied for its role in improving mitochondrial function in oocytes. Preliminary studies suggest that supplementation with CoQ10 may enhance ovarian response and oocyte quality in poor responders.
- As per IFS POR Guidelines, adjuvant use of Co-Enzyme Q10 (CoQ10) in ovarian stimulation is not recommended for poor responders (Caballero et al., 2016; Showell et al., 2020; Xu et al., 2018; Zhu et al., 2023).

3. Individualized Protocol Adjustments

a. Tailoring Protocols Based on Previous Cycles:

- Reviewing and adjusting stimulation protocols based on the response in previous cycles can help optimize outcomes. This might include changes in gonadotropin type, dosage, or the addition of adjuvant therapies.

b. Modified Natural Cycle IVF:

- This approach involves minimal stimulation and aims to retrieve one or two oocytes that are naturally selected and of potentially higher quality. It is less invasive and can be repeated over several cycles to accumulate embryos.

c. Mild Stimulation Protocols:

- Mild stimulation involves lower doses of gonadotropins and aims to balance the number of retrieved oocytes with minimal side effects. Recent evidence suggests that mild stimulation can be effective in poor responders, providing a more patient-friendly alternative to traditional high-dose protocols.

- The decision to use clomiphene citrate alone as a mild stimulation strategy in poor responders may be considered based on patient characteristics and previous treatment response. Mild stimulation with oral clomiphene citrate in combination with low-dose gonadotropin or conventional stimulation is equally recommended in poor responders (Bechtejew et al., 2017; Montoya-Botero et al., 2021).

d. Triggering Ovulation:

- Using a dual trigger (combining hCG and a GnRH agonist) can improve oocyte maturation and potentially enhance embryo quality.

- As per IFS Guidelines, Dual trigger (combining GnRH agonist and human chorionic gonadotropin [hCG]) and conventional hCG trigger are equally recommended for poor responders in GnRH antagonist cycles (Haas et al., 2019; Keskin et al., 2023; Mutlu et al., 2022; Ren et al., 2022; Sloth et al., 2022; Tulek et al., 2022; Zhou et al., 2022).

4. Laboratory Techniques

a. Oocyte/ Embryo Pooling/ Accumulation:

- For women with a very poor response, accumulating oocytes over multiple cycles before fertilization can increase the number of embryos available for transfer.

b. **Preimplantation Genetic Testing (PGT):**

- PGT can help identify embryos with the best implantation potential by screening for chromosomal abnormalities. This technique allows for the selection of the most viable embryos, potentially improving success rates in poor responders.

- As per IFS Guidelines, PGT-A is not recommended for routine use in poor responders, PGT-A requirement needs to be individualized.

Conclusion

Managing unexpected poor responders in IVF requires a multifaceted and individualized approach. The POSEIDON classification provides a valuable framework for categorizing and tailoring treatments to these patients. By optimizing stimulation protocols, incorporating adjunctive treatments, and leveraging the latest evidence and laboratory techniques, clinicians can enhance the chances of successful outcomes for women facing this challenging scenario. Ongoing research and personalized medicine approaches hold promise for further refining these strategies and improving the prognosis for unexpected poor responders in IVF.

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Genetics Involved in Poor Ovarian Responders: Latest Evidence and Research

Introduction

Poor ovarian response (POR) to ovarian stimulation in in vitro fertilization (IVF) is a significant challenge, impacting the likelihood of successful outcomes. Understanding the genetic factors that contribute to POR can provide insights into its etiology and inform personalized treatment strategies. Recent advances in genetic research have shed light on the complex interplay of genetic variants that may predispose individuals to POR. This article reviews the latest evidence and research on the genetics involved in poor ovarian responders.

Defining Poor Ovarian Response

Poor ovarian response is typically characterized by the retrieval of a low number of oocytes despite adequate ovarian stimulation. The Bologna criteria and the POSEIDON classification system provide frameworks for diagnosing and categorizing POR based on ovarian reserve markers and previous responses to stimulation. Despite these classifications, the underlying genetic factors contributing to POR remain a subject of ongoing research.

Genetic Factors and Poor Ovarian Response

1. FSHR and LHCGR Genes

a. Follicle-Stimulating Hormone Receptor (FSHR) Gene:

- The FSHR gene plays a crucial role in the regulation of follicular development and ovarian response. Variants in the FSHR gene, particularly single nucleotide polymorphisms (SNPs), have been associated with variations in ovarian response to stimulation.
- **Key Variants:** The two most studied SNPs, rs6165 (Ala307Thr) and rs6166 (Asn680Ser), have been linked to altered receptor function and sensitivity to FSH, influencing ovarian response.

b. Luteinizing Hormone/Chorionic Gonadotropin Receptor (LHCGR) Gene:

- The LHCGR gene is involved in the regulation of luteinizing hormone (LH) and human chorionic gonadotropin (hCG) signaling, critical for ovulation and luteal function.
- **Key Variants:** Variants such as rs2293275 (Asn312Ser) have been studied for their impact on receptor sensitivity and ovarian response, with some evidence suggesting associations with POR.

2. AMH and AMHR2 Genes

a. Anti-Müllerian Hormone (AMH) Gene:

- AMH is a marker of ovarian reserve, and its levels correlate with the quantity of remaining follicles. Variants in the AMH gene can influence its production and activity.
- **Key Variants:** Polymorphisms in the AMH gene have been studied, but their direct impact on POR remains an area of ongoing investigation.

b. Anti-Müllerian Hormone Receptor Type 2 (AMHR2) Gene:

- AMHR2 mediates the effects of AMH on follicular development. Genetic variations in AMHR2 can affect receptor function and ovarian response.
- **Key Variants:** SNPs such as rs2002555 have been explored for their potential role in ovarian reserve and response to stimulation.

3. CYP19A1 Gene

a. Cytochrome P450 Family 19 Subfamily A Member 1 (CYP19A1) Gene:

- The CYP19A1 gene encodes aromatase, an enzyme crucial for estrogen biosynthesis. Variants in CYP19A1 can influence estrogen production and ovarian response.
- **Key Variants:** Polymorphisms in the CYP19A1 gene, such as rs2414096, have been associated with variations in ovarian response, potentially contributing to POR.

4. Other Genetic Factors

a. ESR1 and ESR2 Genes:

- These genes encode estrogen receptors (ERα and ERβ), which play significant roles in follicular development and ovarian function. Genetic variations in these receptors can impact estrogen signaling and ovarian response.
- **Key Variants:** Polymorphisms in ESR1 (e.g., rs2234693) and ESR2 (e.g., rs1256049) have been studied for their associations with ovarian response and POR.

b. BMP15 and GDF9 Genes:

- These genes encode oocyte-derived growth factors essential for folliculogenesis. Variants in BMP15 and GDF9 can affect oocyte quality and ovarian response.
- **Key Variants:** Polymorphisms such as BMP15 rs3810682 and GDF9 rs254286 have been linked to variations in ovarian response.

Latest Evidence and Research

Recent studies have utilized advanced genetic techniques, such as genome-wide association studies (GWAS) and next-generation sequencing (NGS), to identify novel genetic variants associated with POR:

- **GWAS Studies:** GWAS have identified several loci associated with ovarian reserve markers and response to stimulation. These studies highlight the polygenic nature of POR, involving multiple genetic factors.
- **Whole-Exome Sequencing (WES):** WES has been employed to identify rare genetic variants that may contribute to POR. These findings can provide new insights into the underlying genetic architecture of POR.
- **Epigenetics:** Emerging research on epigenetic modifications, such as DNA methylation and histone modifications, suggests that epigenetic factors may also play a role in ovarian response and reproductive aging.

Personalized Treatment Approach

Understanding the genetic basis of poor ovarian response allows for a more personalized approach to treatment. By analyzing the patient's genetic profile, clinicians can:

1. Identify the genetic cause of POR: Genetic testing can help diagnose the underlying genetic factors contributing to poor ovarian response.
2. Determine the most suitable medication: Based on the patient's genetic profile, clinicians can select the gonadotropins and adjust the dosage to optimize ovarian response.
3. Improve treatment outcomes: Personalized treatment based on genetic factors may lead to an increased number of retrieved oocytes and improved embryo quality, ultimately enhancing the chances of successful pregnancy.

Future Research Directions

While significant progress has been made in understanding the genetic basis of poor ovarian response, further research is needed to validate experimental techniques and develop successful individualized treatment regimens. Suggestions for future research include:

1. Large-scale, multicenter studies: Utilizing large datasets and international registries to increase the number of observations and improve the quality of association studies.
2. Pharmacogenomic approaches: Investigating whether individualized treatment based on genetic profile can lead to improved ovarian stimulation outcomes compared to standard approaches.

3. Correlation between genetic background and ovarian response: Examining the relationship between the "global genetic background" assessed by SNP genotyping, exome sequencing, or whole-genome sequencing and ovarian response.

In conclusion, genetics plays a significant role in determining ovarian reserve and response to stimulation in poor responders. By identifying specific genetic variants associated with POR and adopting a personalized treatment approach based on genetic factors, clinicians can potentially improve outcomes for this challenging patient population. However, further large-scale studies are necessary to validate current findings and develop more effective individualized treatment strategies.

Conclusion

The genetic landscape of poor ovarian response is complex and multifaceted, involving multiple genes and their interactions. Advances in genetic research have provided valuable insights into the etiology of POR, identifying key genetic variants that influence ovarian response. Understanding these genetic factors can inform personalized treatment strategies, potentially improving outcomes for women with POR. Ongoing research and the integration of genetic and epigenetic data will continue to enhance our understanding of POR and pave the way for more effective interventions in reproductive medicine.

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