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波塞冬组3人群的临床研究进展

——波塞冬组3人群临床特征分析

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摘　要

波塞冬标准(Patient-Oriented Strategies Encompassing Individualized Oocyte Number, POSEIDON)是将反应卵巢状态的质量和数量指标结合后对卵巢低反应人群(Poor Ovarian Response, POR)进行分组的方式。在此标准下，波塞冬组3人群被定义为：患者年龄 < 35岁且AFC < 5枚，AMH < 1.2 ng/mL。既往研究普遍认同年龄增大是导致卵巢储备降低最关键的因素，但波塞冬组3人群却表现出年轻但卵巢储备功能低下的特点，辅助生殖技术(Assisted Reproductive Technology, ART)助孕结局不佳。因此通过对该人群的治疗前人群特征、治疗周期特征、妊娠并发症等方面进行综述，以期更好的满足波塞冬组3患者的生育需求，达到更好的ART效果。

关键词

波塞冬标准，卵巢低反应，辅助生殖技术

Clinical Research Progress of POSEIDON Group 3 Population

—Analysis of the Clinical Characteristics of the POSEIDON Group 3 Population

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Abstract

Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) is a classification method that combines both quality and quantity indicators reflecting ovarian response to categorize women with poor ovarian response (POR). Under this standard, the POSEIDON Group 3 is defined as patients who are under 35 years of age, with an antral follicle count (AFC) of less than 5 and an anti-müllerian hormone (AMH) level of less than 1.2 ng/mL. Previous researches generally agree that advancing age is the most critical factor leading to decreased ovarian reserve; however, the POSEIDON group 3 demonstrates a unique profile of being younger yet having compromised ovarian reserve, resulting in poor outcomes in assisted reproductive technology (ART). Therefore, this review aims to summarize the pre-treatment characteristics, treatment cycle features, and pregnancy outcomes and complications of this population in order to better meet the reproductive needs of POSEIDON group 3 patients and improve ART success rates.

Keywords

POSEIDON Stratification, Poor Ovarian Response, Assisted Reproductive Technology

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1. 引言

卵巢低反应(Poor Ovarian Response, POR)是指卵巢对促性腺激素(gonadotropins, Gn)刺激反应不良，表现为卵巢刺激周期发育的卵泡少、血雌激素峰值低、Gn 用量多、周期取消率高、获卵数少和临床妊娠率低[1]。针对 POR 人群较大的异质性，波塞冬(Patient-Oriented Strategies Encompassing Individualized Oocyte Number, POSEIDON)专家组在 2016 年提出 POSEIDON 标准。基于年龄、抗缪勒管激素(Anti-Mullerian Hormone, AMH)、窦卵泡计数(Antral follicle count, AFC)及卵巢既往对 Gn 的反应，POSEIDON 标准将 POR 人群分为 4 组[1]。第 3 组：年龄 < 35 岁、AFC < 5 枚、AMH < 1.2 ng/mL。POSEIDON 组 3 患者在全部符合 POSEIDON 标准女性中仅占 5.2% [2]。考虑到组 3 人群年龄较轻，生育需求较为迫切，但却因未获卵、无可移植胚胎导致的周期取消比例较高[3]，从而在获得卵母细胞的过程中，多数患者需要经历重复的刺激周期，这会对患者的精神和心理造成一定负担。因此，研究波塞冬组 3 人群以改善其临床治疗结局从而满足患者的生育需求、减轻多次卵巢刺激带来的精神、身体和经济负担是十分必要的。现主要综述可能影响 POSEIDON 组 3 患者妊娠结局的人群及治疗周期特征指标，并对不同卵巢刺激方案在组 3 患者中的治疗效果进行讨论。

2. 人群特征

2.1. 年龄及卵巢储备

年龄增加对卵巢储备和妊娠结局的负面影响近年来已得到广泛证实，年龄的增长可能导致女性体内可以发挥功能的线粒体数量减少，线粒体供能不足等[4]。与 30~31 岁的女性相比，34~35 岁女性的生育能力降低了 14% [5]。但大样本研究表明 POSEIDON 组 3 患者的年龄集中在 30.6 ± 2.9 岁[6]，且年龄小于 30 岁的患者占比高达 51.0% [7]，表现为极为年轻化的人群特征。但与此同时，POSEIDON 组 3 人群

却表现出低下的卵巢储备，AFC 小于 4 的患者约占 POSEIDON 组 3 人群的 60.7% [7]，且人群的 AMH 可低至 0.925 (0.685~1.075) ng/ml [8]。

2.2. 体质指数

体质指数(body mass index, BMI)升高可通过改变如胰岛素和脂肪因子等的分布而对女性生殖功能产生不利影响[9]，但 BMI 与卵巢储备的关系存在争议。研究显示[10]女性 BMI 增高与血清 AMH 水平下降有关(coefficient = −0.019, 95%CI [−0.027, −0.010], P < 0.001)。但也有分析认为[11]，高 BMI 是通过抑制卵泡发生和干预卵巢功能实现的，而非真正降低卵巢储备。既往研究显示[2]，符合 POSEIDON 标准患者的 BMI 集中在 22 (20.0~24.5) kg/m^2，显著高于非 POSEIDON 组的女性(P < 0.001)，女性 BMI 是造成人群可归类于 POSEIDON 分组的相关因素(OR = 1.0373, 95%CI [1.0231, 1.0517], P < 0.0001)。但在对 POSEIDON 组 3 患者进一步研究时发现[12]，POSEIDON 组 3 女性与非 POSEIDON 组患者的组间 BMI 无显著差异(22.6 ± 4.0 kg/m^2 vs. 22.5 ± 3.6 kg/m^2, P = 0.087)且 POSEIDON 组 3 中 BMI 大于 25 kg/m^2 的患者仅占总人群的 12.50% [6]。

尽管上述发现显示 POSEIDON 组 3 患者无显著 BMI 升高，但仍应警惕因体重增加造成卵巢储备降低的发生，进一步的研究对于全面地了解 BMI 和 POSEIDON 组 3 人群卵巢储备低下之间的关系至关重要。

3. 治疗周期特征

3.1. 获卵数

Parimala Chinta 等的研究显示[13]，与非 POSEIDON 患者相比，POSEIDON 组 3 患者的获卵数显著减少(3 [2~4] vs. 6 [4~9], P < 0.001)。获卵数是活产率的积极预测因子[14]，累积活产率(Cumulative live birth rate，CLBR)也随获卵数的增多而增加[15] (OR = 5.6, 95%CI [3.1~11.6])。期待对 POSEIDON 组 3 女性给予有效的预处理和制定个体化控制性超促排卵(controlled ovarian hyperstimulation, COH)方案提高每个促排卵周期的获卵数，以期观察其对妊娠结局的影响。

3.2. 双原核胚胎数和优质胚胎数

研究表明[16]，POSEIDON 组 3 女性每个取卵周期所获双原核胚胎数显著低于同年龄段卵巢储备正常且对刺激有反应的患者(4.47 ± 4.26 vs. 10.39 ± 5.09, P < 0.05)，但两组患者表现出相近的受精率(77.91% vs. 78.61%, P = 0.31) [17]，上述特征或许与其相对较低的获卵数有关。然而 POSEIDON 组 3 患者的优质胚胎数却显著低于对照组患者[16] (2.38 ± 2.59 vs. 5.32 ± 3.78, P < 0.05)。优质胚胎移植后的临床妊娠率和活产率均高于低质量胚胎且优质胚胎移植可以显著降低流产率和不良新生儿结局的风险[18] [19]，鉴于胚胎质量与妊娠结局间的多重关联，获得可移植的优质胚胎是 IVF/ICSI 成功的重要因素，因此我们需结合移植策略与患者个体情况制定方案，增加 POSEIDON 组 3 获得优质胚胎的概率，以优化妊娠结局并降低风险。

3.3. 卵巢刺激方案

目前，对 POR 患者采用的常见常规治疗方案包括拮抗剂方案、长方案和超长方案等。以上三种方案在 POSEIDON 组 3 女性中的疗效不一。相较于长方案和拮抗剂方案组，应用超长方案促排卵的 POSEIDON 组 3 女性可获得更高的活产率(31.4 vs. 23.4% vs. 12.6%)，且超长方案组的在获卵数(5.6 ± 3.6 vs. 4.6 ± 3.2 vs. 2.4 ± 1.7, P < 0.001)、可移植胚胎数(2.2 ± 1.6 vs. 1.6 ± 1.6 vs. 1.1 ± 1.1, P < 0.001)上均显著较高[20]；而长方案在周期取消率、活产率等指标上优于拮抗剂方案[21]。与常规刺激方案相比，微刺激方案也可作为

POSEIDON 组 3 女性的促排卵方案之一，该方案虽然不能显著增加人群获卵数和可用胚胎数但却不会增加卵巢刺激引起的胚胎的非整倍体率的风险[22]-[24]，且具有促排卵时间短、Gn 药物用量小等优点。研究表明[25]，尽管拮抗剂组的 POSEIDON 组 3 患者在获卵数(3.68 ± 2.22 vs. 2.75 ± 1.89 vs. 2.48 ± 1.92, P < 0.001)、可用胚胎数(1.75 ± 1.10 vs. 1.26 ± 1.11 vs. 1.28 ± 1.19, P < 0.001)上显著高于甲羟孕酮组和克罗米芬组，但 POSEIDON 组 3 人群的 CLBR 却不受促排卵方案类型的影响。此外，另有 meta 分析显示[26]，微刺激方案的 CLBR 虽与常规刺激方案相近(RR = 1.15, 95%CI [0.73~1.81])，但微刺激方案下的周期取消率却显著增加(RR = 1.48; 95%CI [1.08~2.02])。目前的研究不能支持在 POSEIDON 组 3 女性中使用温和刺激方案代替常规方案[27]。鉴于 POSEIDON 组 3 女性对于卵巢刺激的良好反应性[7]，期待多中心大样本的研究进一步探索 POSEIDON 组 3 女性适用的卵巢刺激方案，以优化治疗效果。

4. 妊娠结局及妊娠期并发症

4.1. 流产率

现流产发生与卵巢储备降低的关系不明，35 岁以下女性的流产发生率为 9.8%~15.8% [28]。有研究表明[29]，低 AMH 水平低于 1.9 μg/L 不会显著增加早期妊娠丢失的风险(AMH < 1.0 μg/L; RR = 0.86, 95%CI: [0.68~1.10], AMH: 1.0~1.9 μg/L; RR = 1.01, 95%CI [0.86~1.27])。但也有部分研究表明流产率增加与低卵巢储备有关，血清 AMH 水平是一项独立于年龄和获卵数的 IVF-ET 流产危险因素(OR= 0.93, 95% CI [0.87~0.99])，患者的血清 AMH 水平处于 0.08~1.60 ng/mL 时，患者流产率显著增加[30]。年龄小于 35 岁且血清 AMH 浓度为 0.5~1.96 ng/mL 的女性行 ART 后的流产风险显著增高(OR = 1.24; 95%CI [1.06~1.44]；P < 0.007) [31]。Parimala Chinta 等的研究证实[13]，POSEIDON 组 3 女性的流产率与非 POSEIDON 人群相近(14.3% vs. 16.5%, P > 0.05)。POSEIDON 各组与卵巢反应正常组间的流产率均无统计学差异(P = 0.059) [7]。

目前关于卵巢储备降低对流产的影响尚无定论，各研究在卵巢储备降低和流产的定义上不能达成一致是导致该结果的原因之一。现有研究显示 POSEIDON 组 3 女性的流产率较卵巢储备正常的人群无统计学差异，这或许是因为 POSEIDON 组 3 患者的平均年龄小，卵母细胞质量尚不受到明显影响[32]所致。

4.2. 活产率

第 1 周期 IVF/ICSI 助孕治疗的 POSEIDON 组 3 人群的活产率(Live, birth rate, LBR)为 29% [33]。相较于卵巢储备正常的女性，POSEIDON 组 3 患者的 LBR 显著降低(30% vs. 34.7%, P = 0.004) [12]。但随着冻融胚胎移植的广泛应用，活产率仅能评估单次胚胎移植后的妊娠结局，在评估人群助孕结局方面已不够全面和理想，因此我们研究了 POSEIDON 组 3 女性的 CLBR，以期对人群的治疗结局进行更综合的评估。

4.3. 累积活产率

CLBR 是一项综合反映一次卵巢刺激后所有新鲜和冷冻胚胎移植的结局的良好评价指标。在对失访患者进行排除的情况下，POSEIDON 组 3 患者的 CLBR 为 35.07%~35.5% [7] [34]。也有研究考虑了仍有未移植的冻存胚胎或未返医院行后续治疗情况下患者的妊娠结局从而计算保守 CLBR (假设此类中断辅助生殖治疗的患者的活产机会为零)和乐观 CLBR (假设此类中断辅助生殖治疗的患者与继续治疗的患者有相同的活产机会)，相较于前种计算方式，计算乐观和保守 CLBR 可以更准确而全面的评估患者助孕治疗的成效。POSEIDON 组 3 患者第 1 个完整周期的累积活产率为 14.73% [6]，在≥6 个完整周期后，乐观 CLBR 和保守 CLBR 的值分别达到 58.12%和 29.76%。相较于非 POSEIDON 组，POSEIDON 组 3 女性的 CLBR 降低了约 30% [35]，POSEIDON 组 3 女性的 CLBR 显著低于非 POSEIDON 患者(31.4% vs. 44.5%, P < 0.05) [12]。对失访人群的处理方式不同，是 POSEIDON 组 3 女性的 CLBR 数值彼此间差异较大的原

因之一。

CLBR 有助于帮助 POSEIDON 组 3 人群在助孕开始前对治疗的有效性和安全性进行评估，增强患者依从性，减少脱落，提高治疗效率[36]。

5. 结语

POSEIDON 组 3 人群为预期低预后人群，不易获得足够数量的卵细胞，所获双原核胚胎数和优质胚胎数均显著低于卵巢储备正常女性。目前选择何种 COH 方案以提高 POSEIDON 组 3 人群治疗的有效性仍然是临床工作者面临的一大挑战，但由于 POSEIDON 组 3 人群的发生率低及划分该人群的 POSEIDON 标准提出时间尚短，在 COH 方案的选择方面缺乏足够数量的大样本临床试验和随机对照研究来支持和贯彻个体化治疗。临床医生可在治疗前评估并告知 POSEIDON 组 3 患者可能的活产率，与患者充分沟通，提高治疗效率。今后仍需在严格执行 POSEIDON 标准的前提下对人群进行研究，以帮助患者获得更理想的妊娠结局。

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