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Oocyte Accumulation In Low-Ovarian Reserve Women: Do Or Not To Do?

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Abstract

Ovarian Poor responder women could be defined as those who have a small number of follicles, usually less than three follicles retrieved after one cycle of ovarian stimulation. Poor responders were classified over time in multiple ways, from the Bologna classification to the recent POSEIDON groups. The oocyte accumulation technique could greatly help poor responder cases; the more oocytes could be retrieved, the better the results are regarding success rates or different tests that need to be done to have euploid-healthy embryos. Going through different studies regarding such an important topic could be a game changer as regards studying the effect of old age on ovarian stimulation, choosing suitable stimulation protocols, managing the outcome of ART through excluding aneuploid embryos, and having enough embryos for that. So, the keyword would be ACCUMULATION, especially for candidates for PGT-A, which can be obtained through repeated stimulation cycles using a cost-effective method such as progesterone primed protocol.

Keywords: IVF; basket; poor responders; POSEIDON; PGT-A

Introduction

Poor ovarian responder women suffer from low oocytes in the stimulated cycles. Poor responders in the Poseidon 4 group have another problem: oocyte quality. Women older than 40 suffer from both quality and quantity of oocytes. Many trials were adopted to increase the number of oocytes by changing the stimulation protocol or increasing the dose.

Till now, there has been no significant improvement in the prognosis of these women. Preimplantation genetic testing for aneuploidy (PGTA) may help these patients to choose the best embryo for transfer. PGTA needs a large number of embryos to select the best. Oocyte accumulation may

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Mini Review

offer a good chance for this cohort of patients suffering from poor ovarian response (1).

This review aims to answer whether oocyte accumulation is effective and safe for poor ovarian responder women.

Poor Ovarian Reserve; Definition And Diagnosis

Poor ovarian response (POR) is a term used in the definition and consensus of the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) and the European Society for Reproduction and Embryology (ESHRE) (2,3). Most POR definitions refer to either a number of follicles of (≤3) on the day of oocyte maturation trigger or a number of oocytes of (≤3) retrieved after an ovarian stimulation cycle. There was no widely accepted consensus on the diagnostic criteria for POR until ten years ago. The word POR has been defined in excess of forty ways in current literature. The Bologna classification from the ESHRE consensus on the characterization of poor response to OS in vitro fertilization (IVF) (2) describes POR's first widely accepted description. The patient who forms the basis of the Bologna categorization has already completed an OS cycle.

Nonetheless, the categorization recommends classifying the patient as a predicted POR patient if OS has not occurred. The Bologna criteria have been criticized for failing to define risk factors precisely, ignoring the importance of oocyte quality, and most importantly for causing a notable amount of variability among patients who have received a diagnosis based on the criteria (1). The POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) categorization method for POR is more recent (4- 6). The advantages of this categorization method include a more comprehensive approach that incorporates both qualitative and quantitative data and a more robust stratification scheme for POR patients. Moreover, data indicates that the POSEIDON classification's significance in stratifying POR patients is supported because cumulative live birth rates after IVF varied between the various POSEIDON groups (7).

Aneuploidy Rate and Poor Quality And Quantity Oocytes In Poor Responders

Trisomic pregnancies, losses, and infertility are more common in women of advanced maternal age (AMA, age > 35) (8). According to Fuentes et al., they also show diminished ovarian reserve (DOR) and poor ovarian responses (POR) to gonadotropin stimulation in assisted reproduction (9). The main reason for decreasing oocyte and embryo quality and decreased rates of conception and live birth in AMA women is oocyte and embryo aneuploidy. Cohesin dysfunction, telomere shortening, spindle instability, aberrant checkpoint control, decrease in preimplantation embryo development rates to the blastocyst stage, age-related hormonal aberrations and mitochondrial dysfunction are considered to be the mechanisms underlying these processes (10). After adjusting for age, blastocysts from POR cases are less likely to be euploid than those from women with normal ovarian reserve. This finding is corroborated by a study by Mandy G. et al. that evaluated the association between the incidence of aneuploid blastocysts and hormonal parameters of diminished ovarian reserve.

The patients who suffered from POR had more aneuploid blastocysts with a percentage of (66% compared with 51.7%; P<.05) and all aneuploid blastocyst cycles (35.1% compared with 14.3%; P<.001) than patients with normal ovarian reserve. Nonetheless, implantation rates were comparable after the transfer of euploid blastocysts (69% vs. 61.7%; not significant) (11).

To determine if trisomy cases were more likely than controls to have a history of ovarian surgery and to respond less strongly to ovarian hyperstimulation, Haadsma M.L. et al. conducted case-control research. They discovered a correlation between retrieving less than four oocytes during IVF treatment (OR 4.0; 95% CI: 1.4–11.5; P = 0.01) and trisomic pregnancy and ovarian surgery history [odds ratio (OR) 3.3; 95% confidence interval (CI): 1.0–10.5; P = 0.04]. Based on these findings, they proposed that women undergoing IVF who have a reduced ovarian follicle pool are more likely to experience a trisomic pregnancy,

regardless of their age (12). Additionally, E.G., Jaswa et al. discovered that, regardless of age, there were no changes in the LBR between patients with and without POR following euploid single-embryo transfer and that euploid rates were much lower among women with versus without POR (29.0% vs. 44.9%) (13).

The Effect of Age and AMH Level on ART Outcomes in Patients with Reduced Ovarian Reserve

The most significant indicators of having at least one euploid blastocyst and the overall number of euploid blastocysts are ovarian reserve and female age. It has previously been demonstrated that the blastocyst euploidy rate among ART-undergoing women decreases dramatically with increasing female age and that the size of the blastocyst cohort affects the overall number of euploid embryos. According to Hosseinzadeh F et al., participants under 35 years old had higher levels of dominant follicles, MII oocytes, grade A and B embryos, serum estradiol level, gonadotropin level, AMH, biochemical pregnancy, clinical pregnancy, and live birth rate. Additionally, the chance of retrieving more than three oocytes was 97.1% lower in individuals over 35 than in those under 35 (14). Additionally, between 2017 and 2020, 847 consecutively recruited couples about to undergo their first preimplantation genetic testing for aneuploidies (PGT-A) cycle were included in a prospective analysis by La Marca A et al. Following oocyte insemination and ovarian stimulation, 40.1% of couples developed a blastocyst ready for the PGT-A. 33.6% of the 1068 blastocysts examined were euploid. In particular, it was shown that there was a negative correlation between the result and female age and a positive correlation between the outcome with AMH (15).

Additionally, Arnanz A et al. demonstrated that all patients with AMH less than 0.65 ng/ml as well as patients with AMH 0.65-1.29 ng/ml had an impact on the likelihood of having at least one blastocyst biopsied/stimulated cycle (1156/1410), the likelihood of having at least one euploid blastocyst/stimulated cycle (880/1410), and the likelihood of having one euploid blastocyst once biopsy was completed (880/1156). Patients having reduced ovarian reserve (AMH < 1.3 ng/ml) are less likely to have at least one blastocyst biopsied and less likely to have at least one euploid blastocyst each ovarian stimulation cycle, regardless of age (16).

Oocyte Accumulation

According to Stoop et al. (2012), 3.83% of all recovered mature oocytes end up as LBs. According to the authors, the ovarian response between the ages of 23 and 37 determines the oocyte usage rate (number of LBs per mature oocyte) to a significantly smaller extent than age. However, beyond age 38, ovarian response was less important in determining the oocyte usage rate, and age was more important (17).

Between 23 and 37 years, the average oocyte utilization rate stayed around 4.5%. However, after 38 years, the oocyte usage rate decreased considerably, falling from 3.8% at 38 years to 0.8% at 43 years ($P < 0.001$) (Stoop et al.2012) (17). Moreover, Fatemi et al. (2013) demonstrated how the average number of high-quality embryos rose in proportion to the ovarian response, rising from 1.1 in the case of 0–5 retrieved oocytes to 8.0 in the case of >18 retrieved oocytes (recombinant FSH group). Therefore, with the ovarian response, the number of cryopreserved embryos likewise increased from 0.2 with 0–5 oocytes to 4.2 with >18 oocytes (18).

There is no conclusive data yet regarding the beginning of the second stimulation cycle. In certain research, traditional stimulation is initiated just after the onset of spontaneous menstruation. However, another technique is to utilize a combination of oral contraceptive tablets or vaginal micronized progesterone in the luteal phase following the first ovum pick-up to assist suppression of the FSH rise and help initiate the next stimulation cycle as soon as feasible to shorten the duration of the desired number of oocytes (19).

Outcomes Of ART In Accumulation Cycles

Compared to women who had a single IVF cycle with fresh transfer, the cumulative live

birth rate per woman was considerably higher in the first study on oocyte/embryo published in 2012 (36.4% vs. 23.7%). Others concluded that accumulating embryos through three NM-IVF cycles before transfer increases live birth rates and lowers the likelihood that poor responders aged 35 and older won't have an embryo for transfer since the study strategy resulted in considerably higher live birth rates (20- 21).

However, as compared to no embryo banking, some data indicated that women having IVF with POR who banked their embryos had a considerably lower cumulative live birth rate and a significantly longer time to live delivery. Compared to the non-banking group, the banking group's cumulative live birth rate (CLBR) was much lower (22). These results may be due to technical points in the freezing and thawing steps, which may affect the pregnancy rate. Greco Et al. showed that in contrast to repetitive single embryo transfers in a fresh modified natural cycle, the co-transfer of embryos developed from vitrified oocytes accumulated during previous modified natural cycles and an embryo developed from the most recent fresh modified natural cycle assures an excellent clinical outcome with a significantly higher overall and clinical pregnancy rate (23).

A. Cobo et al. provided evidence that the treatment is a successful alternative for LR patients by showing that the accumulation of oocytes through vitrification for low responders is linked to a lower dropout rate, fewer transfer cancellations, higher LBR per intention-to-treat patient, more cycles with vitrified embryos, and higher cumulative LBR (20). The results of ART for poor responders are improved by oocyte accumulation and embryo accumulation. Pregnancy rates might be raised by transferring enough embryos utilizing frozen, thawed embryo transfer (ET) and obtaining embryos from POR patients using numerous COS, natural, or modified natural procedures, as Jieun Shin et al. showed in their retrospective analysis (24).

PGT-A In Poor Responders

As demonstrated by earlier research, poor responder patients, particularly those in Poseidon group 4, had low blastocyst and oocyte quality and quantity. It is advised to use PGT-A to select the euploid blastocyst and enhance implantation to shorten the pregnancy time for this group of women (25-26).

The effectiveness of oocyte cryopreservation has increased significantly since the introduction of the vitrification technique, which uses rapid cooling rates to avoid ice formation (27–28), which is now a reliable and safe method that produces results similar to those observed in new cycles. It has been widely shown that there is a clear relationship between the number of embryos available for selection and the success rate following a PGT-A cycle. A low number of embryos for genetic study is rather common in PGT-A cycles, and one of the main conditioning variables is the number of mature oocytes extracted (29–30).

To accumulate sufficient oocytes in PGT-A cycles with oocyte accumulation, two or more consecutive oocyte retrieval cycles with vitrification are suggested. A final cycle with vitrified and fresh oocytes is anticipated to produce more embryos for examination (31-32). However, there is no sufficient evidence on the efficacy of this technique in the form of the PGTA cycle outcome.

A retrospective examination of 95 PGT-A cycles, including oocyte accumulation and vitrification, was conducted by Parriego M et al. in patients who had recovered less than ten metaphase II oocytes in the first cycle. After MII oocytes were vitrified, an additional round of ovarian stimulation was carried out. Fresh and warmed MII oocytes were handled as a single cohort. D3 underwent embryo biopsy, and single blastomeres were examined by array-CGH analysis. On D5, a euploid embryo transfer was carried out. He concluded that PGT-A patients' oocyte accumulation allows for a rise in oocyte count without causing aneuploidy and, consequently, an increase in embryos for study. However, he discovered a reduced euploid blastocyst / MII oocyte ratio, a sign of lower oocyte efficiency during vitrification (33). Oocyte accumulation, according to J Rodriguez-Purata and F Martinez, improves the result and allows women who have inadequate response to be compared to normal responders in PGTA (34).

According to Labarta et al., the cumulative likelihood of establishing an LB does not plateau at any ovarian response level, reaching values above 75% in the extremely high response (>30 oocytes). The number of euploid embryos rises proportionately to the number of retrieved oocytes.

As a result, the recommended approach in PGT cycles is a stimulation plan that seeks to maximize the ovarian response while minimizing the risk of side effects for the patient (35). In a prospective investigation, Sandrine Chamayou et al. used tropho-ectoderm embryo biopsy to compare frozen and fresh oocytes from the same women following injection and PGTA. They discovered that blastocysts do not become aneuploid due to oocyte vitrification or heat. There were 9.6% and 11.4% of euploid blastocysts per injected frozen egg and fresh oocyte, respectively, on average ($p>0.05$). ICSI can improve the number of viable euploid embryos for transfer by combining fresh oocytes with accumulated vitrified oocytes. The frequencies of euploid blastocyst implantation in fresh and frozen oocytes were similar ($p > 0.05$; 56.0% from thawed oocytes versus 60.9% from fresh oocytes) (36). The same conclusion was supported by Alexia et al.'s retrospective analysis, which discovered that repetitive ovarian stimulation combined with cumulative oocyte or embryo vitrification might improve the likelihood of a successful pregnancy for low-responder patients enrolling in a PGD program (37).

Stimulation Protocols In Poor Responders

In its practice committee opinion, ASRM concluded that, when compared to traditional IVF stimulation protocols, mild ovarian stimulation (low-dose gonadotropins with or without oral agents) should be strongly considered for patients who are poor responders and intend to pursue IVF, as it is less expensive and has comparable low pregnancy rates (38). Random start protocol: based on the multiple follicular recruitment idea, stimulation can begin at any point throughout the cycle. Oocytes extracted from random start cycles are similar to those extracted from conventional cycles, particularly in patients who are poor responders. Random start works well for cancer patients in fertility preservation programs and poor responders (39).

Follicle start is one of the random start techniques; it produces an oocyte yield equivalent to conventional stimulation. The proportion of euploid blastocyst, which measures oocyte competency, was similar in follicular and luteal oocytes (40). Dual stimulation—follicular stimulation followed by ovum pick-up and luteal stimulation—may shorten the time needed to produce the right number of oocytes (41).

According to Yanqun Luo et al., more oocytes were recovered from the luteal phase than the follicular phase. Additionally, he suggests using a GnRH agonist or rec HCG to induce ovulation instead of urine HCG (42). However, from September 2018 to March 2021, N. Massin et al. carried out a multicenter, open-labeled, randomized controlled trial (RCT) in four IVF centers to examine the quantity of oocytes recovered from duostim and two consecutive antagonist cycles. They concluded that duostim was not superior to two antagonist cycles in a row (43). Another barrier to the widespread application and use of duostim is the absence of a cost-effectiveness analysis (44).

Progesterone Primed Ovarian Stimulation (PPOS) In Poor Responders

The adoption of the PPOS procedure in elderly IVF patients should be carefully assessed to guarantee acceptable obstetrical and neonatal outcomes despite the benefits of a lower cost and easier medication administration. For infertile individuals 38 years of age and older, the PPOS protocol produces a euploidy rate that is four times lower than that of the traditional GnRH-antagonist regimen. Earlier research that contrasted PPOS with alternative methods has yielded inconsistent findings (45).

Progestin stimulation may have adverse consequences on oocyte competence, embryo availability, embryo implantation, and obstetric outcome despite PPOS's effectiveness. This is particularly concerning for patients who

struggle to achieve a positive outcome from IVF. Furthermore, reports have shown that the PPOS technique produces fewer recovered oocytes (46). Compared to the GnRH-antagonist treatment, the PPOS technique may cause a greater cycle cancellation rate and a lower cumulative live birth rate in specific patient groups (47). Before the PPOS procedure is widely used, more research on its effectiveness in a broader population is required to help determine which patient population is most suited.

Conclusion

We can conclude that oocyte accumulation may benefit poor ovarian reserve patients; it may help decrease the dropout rate in ART cycles. The best solution for poor ovarian reserve women who are candidates for PGTA is accumulation. The progesterone-primed cycle may be a patient-friendly, cost-effective stimulation protocol for oocyte accumulation. Further studies are needed to assess the cost-benefit of its application.

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