DOUBLE STIMULATION PROTOCOL TO IMPROVE PREGNANCY RATE IN POOR RESPONDERS UNDERGOING ICSI

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INTRODUCTION

The infertile patients with aging ovaries—also sometimes referred to as impending primary ovarian insufficiency (POI), impending premature ovarian failure (POF), or poor ovarian responders (POR), constitute a significant bulk of the patients appealing to IVF/ART (1–3). The prevalence of this group of patients seems to be increasing, due to many patients postponing conceptions to the late thirties or even beyond the age of forty. In over half of these patients, no etiologic cause can be pinpointed (1–3). Whereas depletion of most of the ovarian follicles due to older age is well documented, there are several other etiologies associated with poor ovarian reserve (1–3). Among the identified etiologies, different causes including chromosomal and genetic etiology (1, 4–8), and metabolic (4, 9, 10), enzymatic (4, 9, 10), iatrogenic (4, 11), toxic (1–8), autoimmune (1–4), and infectious causes (1, 2, 4–6, 9).

Although the most successful and ultimate treatment of POI/POF/POR patients is egg donation (ED), many, if not most, of these infertile women are reluctant to consent to ED upon the initial diagnostic inter-view, requesting alternative solutions despite the low odds for success (1–3).

Although no unequivocal definition of the poor responders has been universally accepted, the Bologna classification defines poor responders by two of the following characteristics:

- Maternal age 40 years or older, or other risk factors for poor ovarian response (such as excision of bilateral ovarian endometriomas),
- Poor ovarian response in previous IVF cycle(s) (retrieval of three or fewer oocytes in a conventional stimulation IVF protocol), and
- Low antral follicle count (AFC) (less than 5–7 follicles), or low anti-Müllerian hormone (AMH) below 0.5–1.1 ng/ml (3.5–8 pmol/L) (19).

More recently, a new classification of poor ovarian reserve patients in IVF/ART has been put forward by the POSEIDON (Patient Oriented Strategies Encompassing Individualized Oocyte Number) group (20–22).

In this classification, four subgroups have been suggested according to qualitative and quantitative parameters, like the Bologna criteria, namely:

- Age and the expected aneuploidy rate
- Ovarian biomarkers (AFC and AMH), and
- Ovarian response to COS in a previous ART/IVF cycle.

The four POSEIDON classification groups (20) are:

I. **POSEIDON group 1**: Patients younger than 35 years old, with normal markers of ovarian reserve (AMH>1.2 ng/mL, AFC>5), and with an unexpected poor ovarian response (POR).

· Subgroup 1a: <4 retrieved oocytes on conventional COS in ART/IVF cycle,

· Subgroup 1b: 4–9 retrieved oocytes on conventional COS in ART/IVF cycle,

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II. **POSEIDON group 2**: Patients older than 35 years old, with normal markers of ovarian reserve: AMH>1.2 ng/mL, AFC>5, and with an unexpected poor ovarian response (POR).

· Subgroup 2a: <4 retrieved oocytes on conventional COS in ART/IVF cycle,

· Subgroup 2b: 4–9 retrieved oocytes on conventional COS in ART/IVF cycle,

III. **POSEIDON group 3**: Patients younger than 35 years old, with poor ovarian reserve: AMH <1.2 ng/mL, AFC <5,

IV. **POSEIDON group 4**: Patients older than 35 years old, with poor ovarian reserve: AMH <1.2 ng/mL, AFC <5.

The POSEIDON classification concept offers a possibly improved stratification for poor responders, which might potentially improve study design and help to fine-tune prognostication. It presents several possible advantages over previously described models, facilitating the evaluation of strategies that could generate higher success of ART/IVF for specific subgroups of patients. It may, in addition, enable the fertility specialist to more accurately advise their patients regarding their treatment prognosis.

References

1. **Blumenfeld Z. Fertility treatment in women with premature ovarian failure. Expert Rev Obstet Gynecol. (2011) 6:321–30. 10.1586/eog.11.15 [CrossRef] [Google Scholar]**

2. **Blumenfeld Z. Premature ovarian failure: etiology and possible prevention. Expert Rev EndocrinolMetab. (2009) 4:173–81. 10.1586/17446651.4.2.173 [PubMed] [CrossRef] [Google Scholar]**

3. **Blumenfeld Z, Halachmi S, Peretz BA, Shmuel Z, Golan D, Makler A, et al. . Premature ovarian failure–the prognostic application of autoimmunity on conception after ovulation induction. FertilSteril. (1993) 59:750–5. 10.1016/S0015-0282(16)55854-3 [PubMed] [CrossRef] [Google Scholar]**

4. **Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Rev. (1997) 18:107–34. 10.1210/edrv.18.1.0291 [PubMed] [CrossRef] [Google Scholar]**

6. **Simpson JL. Genetic and phenotypic heterogeneity in ovarian failure: overview of selected candidate genes. Ann NY Acad Sci. (2008) 1429:146–54. 10.1196/annals.1429.019 [PubMed] [CrossRef] [Google Scholar]**

8. **Krauss CM, Turksoy RN, Atkins L, McLaughin C, Brown L, Page DC. Familial premature ovarian failure due to an interstitial deletion of the long arm of the 3 chromosome. N Engl J Med. (1987) 317:125–31. 10.1056/NEJM198707163170301 [PubMed] [CrossRef] [Google Scholar]**

9. **Chen YT, Mattison DR, Feigenbaum L, Fukui H, Schulman JD. Reduction in oocyte number following prenatal exposure to a diet high in galactose. Science. (1981) 214: 1145-7. 10.1126/science.7302587 [PubMed] [CrossRef] [Google Scholar]**

10. **Forges T, Monnier-Barbarino P, Leheup B, Jouvet P. Pathophysiology of impaired ovarian function in galactosaemia. Hum Reprod. (2006) 12: 573–84. 10.1093/humupd/dml031 [PubMed] [CrossRef] [Google Scholar]**

11. **Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod. (2008) 14:543–52. 10.1093/humupd/dmn022 [PubMed] [CrossRef] [Google Scholar]**

19. **Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria. Hum Reprod. (2011) 26:1616–24. 10.1093/humrep/der092 [PubMed] [CrossRef] [Google Scholar]**

20. **Humaidan P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of 'Low prognosis patients in assisted reproductive technology' and its proposed marker of successful outcome. F1000Res. (2016) 5:2911. eCollection. 10.12688/f1000research.10382.1 [PMC free article] [PubMed] [CrossRef] [Google Scholar]**

22. Levi-Setti PE, Zerbetto I, Baggiani A, Zannoni E, Sacchi L, Smeraldi A, et al. . An observational retrospective cohort trial on 4,828 IVF cycles evaluating different low prognosis patients following the POSEIDON criteria. Front Endocrinol. (2019) 10:282. 10.3389/fendo.2019.00282 [PMC free article] [PubMed] [CrossRef] [Google Scholar]